Acute-phase heart rate trajectories and functional outcomes in acute ischemic stroke

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Abstract
The heart rate (HR) trajectory is a dynamic metric that shows how HR changes over time. Previous studies have demonstrated that elevated HR is associated with stroke events. However, little research has been done on the influence of shifting HR throughout the acute period on clinical outcomes. This study aims to investigate the effect of HR trajectories on functional outcomes in patients with acute ischemic stroke (AIS).

A total of 981 AIS patients were included in the study. A latent mixture model was used to assess HR trends over the first 7 days following disease onset. The patients were divided into four groups based on different HR trajectories: markedly decreasing in 48 h (T1), mildly decreasing in 48 h (T2), sustained moderate in 7 days (T3), and sustained high in 7 days (T4). Poor outcome was defined as a modified Rankin Scale (mRS) score of ≥3 in 3 months. Logistic regression was used to analyze the correlation between different HR trajectories and outcomes. The incidence of poor outcomes was 9.02%, 10.80%, 11.79%, 16.36% in T1 (n = 133), T2 (n = 352), T3 (n = 441), and T4 (n = 55) groups, respectively. Compared with T1 group, T4 group was significantly associated with a higher risk of poor outcome at 3 months (odds ratio = 3.00, 95% confidence interval = 1.06–8.54, p value = .0392). This suggests that in AIS patients, a sustained high HR trajectory is linked to a greater likelihood of poor functional outcome than a markedly decreasing HR trajectory. HR trajectories demonstrate the utility of repeated HR measurements for outcome assessment.

KEYWORDS
acute ischemic stroke, functional outcome, heart rate trajectory

1 | INTRODUCTION

Many studies have proven that heart rate (HR), as a readily measured and intervenable cardiovascular parameter, may be used to predict unfavorable cardiovascular disease outcomes irrespective of established risk variables.1–3 The HR of normal adults is affected by sympathetic and parasympathetic nerves,4 showing different trajectories with the changing of time. HR trajectory patterns integrate information regarding multiple HR measurements and how they have changed over time. As a dynamic indicator, HR trajectories are of great significance for disease assessment. Different HR trajectory patterns may exist in one population, and these may be associated with different
outcomes. The study on HR and cardiovascular event outcomes is still rife with disagreements. The association between raising or lowering HR and cardiovascular events has been studied in several ways.5−12 Most previous studies on the effect of acute-phase HR on clinical outcomes in acute ischemic stroke (AIS) have used one-time-point HR values as a predictor for the outcome. However, because the direction and magnitude of subsequent HR changes during the acute phase differ among patients, this method has limited predictive potential.

Therefore, this study intends to use the HR data collected in the BOSS (Blood Pressure and Clinical Outcome in TIA or Ischemic Stroke Study) study to first examine the HR trajectory within 7 days of admission to further investigate its correlation with the 3 months functional outcome of AIS patients.

2 | METHODS

2.1 | Study cohort

This study was conducted among patients from the BOSS study, a nationwide, hospital-based, longitudinal cohort.13 2608 patients with newly diagnosed (within 7 days of onset) AIS or TIA were consecutively enrolled from October 2012 to February 2014 at 61 hospitals in China. AIS was diagnosed according to World Health Organization criteria combined with brain computed tomography or magnetic resonance imaging confirmation.14 TIA was defined as symptomatic neurologic deterioration lasting <24 h without new infarction on neuroimaging.15 Patients hospitalized for more than 24 h after stroke onset or who did not complete a 3-month follow-up were excluded from this study, as were TIA patients, patients with atrial fibrillation, patients who received beta-blocker during hospitalization, and patients who received intravenous thrombolysis.

The study was approved by the Central Institutional Review Board at Beijing Tiantan Hospital. Written informed consent was obtained from all the patients or their representatives.

2.2 | HR and blood pressure measurement

Brachial blood pressure (BP) and HR were recorded by trained physicians or nurses according to a standard measurement method recommended by the American Heart Association on the first day of admission.16 The two parameters were monitored twice daily for the following 6 days after admission using a semiautomatic upper-arm BP monitor (HEM403; OMRON Healthcare).16 All patients and their caregivers were trained by the physicians on the use of the device during their stay. After discharge, patients were asked to measure their HR and BP twice a day at home using the monitor mentioned above until 3 months after the stroke onset. All the HR and BP data was recorded.

2.3 | Baseline variables

Baseline information, including age, sex, smoking, alcohol drinking, premorbid modified Rankin scale (mRS), self-report past medical history (stroke, coronary artery disease, hypertension, diabetes mellitus, dyslipidemia), HR and BP at admission, National Institutes of Health stroke scale (NIHSS) at admission, HR variability (based on the standard deviation) within 7 days of disease onset, discharge medications (antiplatelet, antihypertensive, lipid-lowering) were all recorded. All information was obtained by using a nurse-administered standardized questionnaire at the time of admission. History of stroke was defined as previous ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage confirmed by medical records. History of hypertension was defined as previous hypertension and use of antihypertensive medication.

2.4 | Outcome assessment

The primary outcome of this study was defined as mRS ≥ 3 at 3 months. mRS ranging from 0 to 6, a measure of major disability, was obtained by doctors and trained research nurses through face-to-face follow-up.17 A score of 0 indicated no symptoms, a score of 5 indicated severe disability, that is, being bedridden, incontinent, or requiring constant nursing care and attention, and a score of 6 indicated death. Death events were confirmed through death certificates from the local citizen registry or by the attended hospital.18

2.5 | Statistical analyses

Growth curve parameters of HR repeatedly measured during the first 7 days were estimated using a latent mixture model by SAS PROC TRAJ as previously reported.19 For the PROC TRAJ procedure, we adopted the censored normal (CNORM) model because HR is a continuous variable. We initially assumed the trajectory patterns to be cubic and treated HR as a dependent variable and time (days) as an independent variable. The number of trajectory patterns was calculated using the Bayesian information criteria. The number of groups with the highest Bayesian information criterion was considered the appropriate one. In the CNORM model, the minimum for censoring (MIN) was 43, and the maximum for censoring (MAX) was 120.

For descriptive analyses, continuous variables are shown as the mean ± standard deviation or median with interquartile range in cases of skewed distribution, and categorical variables are expressed as a percentage. Baseline variables between different groups were compared using t test, analysis of covariance, Kruskal–Wallis test, nonparametric Wilcoxon test for continuous variables and chi-square test for categorical variables.

The patients were classified into four HR trajectory groups, which included markedly decreasing pattern (T1), mildly decreasing pattern (T2), moderate-stable pattern (T3), and high-stable pattern (T4), based on individual’s linear slope parameters. The differences in trajectory curve parameters between outcome groups were tested by analysis of covariance. The relationship between HR trajectory groups and the outcome was examined in multivariable logistic regression models. Covariates included in the model for adjustment were age, sex, smoking...
status, drinking status, mRS prior to stroke, history of stroke, coronary heart disease, hypertension, diabetes, and hyperlipidemia, NIHSS on admission, SBP on admission, discharge medication use of antiplatelet agents, antihypertensive agents and lipid-lowering agents, and heart-rate variability during 7 days after onset. Odds ratio (OR) and 95% confidence interval (CI) were estimated in logistic regression models. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

In this study, a total of 2608 AIS/TIA patients with complete baseline information from BOSS study were finally eligible. Therein, 1448 patients admitted to hospital within 24 h after onset. After excluding 150 TIA patients, 76 patients with atrial fibrillation and 69 patients who received β-blocker during hospitalization, 981 patients with AIS who had completed baseline and follow-up interview surveys formed the current study cohort. In addition, 150 patients who received intravenous thrombolysis were also excluded from the study since it has been shown to have a significant impact on stroke patients’ functional outcomes. The flowchart of the patient selection is presented in Figure 1. Characteristics of patients included in and excluded from the study were compared in Table S1 in supplement. The baseline characters by the primary outcome have been added in Table S2.

Figure 2 shows trajectory groups of HR measured during the first 7 days after admission. We categorized the study population based on four observed discrete trajectories of HR and changing patterns: participants who started with relatively low HR (median admission HR 68.0 bpm) and experienced markedly decreasing HR in 48 h and finally remained stable, referred to as “markedly-decreasing pattern” (n = 113); participants who started with relatively moderate HR (median admission HR 72.0 bpm) and experienced mildly decreasing HR in 48 h and finally remained stable, referred to as “mildly-decreasing pattern” (n = 352); participants who started with relatively moderate HR (median admission HR 78.0 bpm) and remained stable, referred to as “moderate-stable pattern” (n = 441); participants who started with relatively high HR (median admission HR 80.0 bpm) and
remained stable, referred to as “high-stable pattern” \((n=55)\). The most significant changes in HR occurred within the first 48 h and then remained stable. Among them, T1 group exhibited the most noticeable difference.

Table 1 showed the baseline variables in terms of different HR trajectory groups. The median patient age was 62 years, and 28.54% were female. Patients in T4 group were younger than those in other groups. The prevalence of history of stroke was higher in T3 and T4 groups. The other baseline data in all the groups showed no significant differences.

Table 2 shows the association between HR trajectory groups and functional outcome. The poor functional outcome for the four groups were 9.02%, 10.80%, 11.79%, 16.36%, respectively. Compared with T1 group, T4 group was significantly associated with higher risk of poor outcome even after adjusting for confounders \((OR: 3.00, 95\%CI: 1.06–8.54, p = .0392)\).

4 | DISCUSSION

This study focused on the analysis of acute phase HR trajectory in patients with AIS. We identified that HR changed evidently within 48 h after disease onset and then remained nearly stable for at least 6 days. The sustained high HR in the T4 group was significantly associated with a higher risk of poor functional outcome at 3 months, compared to the markedly decreasing HR in the T1 group.

The initial rise in BP is common in the early phase of ischemic stroke. This phenomenon of elevation in BP within 24 h of disease onset is defined as acute hypertensive response. Without specific antihypertensive therapy, most patients’ BP will drop naturally and gradually recover to prestroke levels.

However, the studies related to HR or HR trajectory during the acute phase of ischemic stroke are relatively rare compared to BP and BP trajectory. A single-center cohort study from Japan revealed that no significant variations of HR were found on the first day and seventh days after disease onset. For analysis of the outcome, most previous studies used a single-point HR measurement, such as the baseline HR. This is the most possible reason for the disagreement in previous studies because the single-point HR do not reflect within-individual changes in HR over time. It is possible that some high-risk people are mistaken for low-risk people. Using the trajectory may help to avoid this kind of mistake. However, no previous studies have suggested that using a long-term HR trajectory has a benefit over using single-point values of HR levels. Only a few studies have identified that BP trajectory predicts cardio-cerebrovascular events better than a single-point BP reading.

We have previously published that the decrease of BP in the acute phase is predictive of favorable outcomes in AIS patients and BP trajectories have a greater power to detect the association than individual BP values at one time-point. We uncovered two recent studies that evaluated the relationship between resting HR trajectories and cardio-cerebrovascular events and mortality. The results revealed that elevated trajectories were associated with an increased risk of myocardial infarction and all-cause mortality, which is basically in line with our findings. We established a HR trajectory model in our study by taking HR data for 7 days in a row. Our study provided evidence that AIS patients with persistently high HR had a higher risk of poor functional outcomes at 3 months.

We found that the HR trajectory changed within 48 h from the stroke onset and then remained steady, indicating that a long trajectory recording might give more thorough and complete. To our best knowledge, no previous study has looked into the short-term (days to months) shifting pattern of HR following a stroke. HR was regulated by both parasympathetic and sympathetic nervous system. When humans are at rest, the parasympathetic nervous system takes over, and HR is mostly governed by vagal tone. Sympathetic nerve system activation from AIS can lead to autonomic instability. This might result from direct damage or compression of specific regions in the brain that mediate autonomic control and other additive factors. Sympathetic overactivity may result in higher HR and BP. The so-called “acute hypertensive response” always occur within 24 h after stroke onset. However, a rise in BP may reflexively cause a decrease in HR. One previous study also suggested that patients with AIS may perform with decrease of cardiac baroreceptor sensitivity. In conclusion, because individual differences in autonomic regulation capacity exist, different trajectories were observed. We may reasonably assume that the rapid shift in HR...
within 48 h is due to the complicated autonomic process mentioned above. The autonomic nervous system gradually finds a balancing point during the next few days, allowing the HR to settle. Basic experimental research are needed to corroborate the findings.

Previous studies have linked high HR to worse cardiovascular outcomes, potentially as a result of prolonged hemodynamic strain on the artery wall, which causes wall stiffness,31–33 as well as an increase in sympathetic tone, which leads to an increase in artery wall pressure and endothelial damage.33 Elevated HR is also associated with platelet activation,34 prothrombotic state, and independently increased risk of hypertension.8 A previous review has summarized several studies in different mouse models and different vascular beds about changing in HR. Mild HR lowering (13%–17%) has been proven to prevent endothelium-dependent vasorelaxation.35 Although no human trials have been performed to investigate if HR reduction is beneficial as a prevention strategy for cardio-cerebrovascular disease. HR trajectories remained independent risk factors for poor functional outcome in AIS patients after adjusting for potential confounding factors, such as medications that affect HR and atrial fibrillation. As a result, we considered that a high-stable HR pattern
might facilitate the advancement of atherosclerosis, thrombosis, and vasoconstriction, finally lead to adverse cardio-cerebrovascular events.

It is worth noting that HR in both the above-mentioned and our studies were essentially all in the normal range (60–100 bpm). However, multiple observation studies have suggested that the change of HR within the normal range still has some impact on the cardiovascular events.1–3 According to a large prospective cohort study, for every 15 bpm rise in HR, the risk of cardiovascular disease increases by 24% in men and 32% in women.1

There is currently no consensus on the importance of a decrease in HR in the prognosis of ischemic stroke. The most widely accepted normal HR varies from 60 to 100 bpm.36 Some studies reported that decline HR in the acute phase have not shown benefits in mortality of ischemic heart disease.10 On the contrary, some studies even suggested that changes in HR were not correlated to coronary artery diseases or other cardiovascular events.11,12 In the present study, most patients’ HR were within the normal range. But the sustained high trajectory pattern was associated with a higher risk of poor functional outcomes than the markedly decreasing pattern.

It is true that the clinical implications of HR and BP trajectories remain unclear. The importance of HR trajectory patterns cannot be overstressed. Since HR and BP are both vital signs, clinical studies on HR are less common than when comparing to BP. Again, we want to draw more researchers’ attention to the importance of HR in individuals with cardiovascular disease. Our findings imply that in clinical practice, special attention should be made to patients with persistently high HR, and that additional research is needed to determine whether early intervention is required in the future.

There were still some shortcomings in this study. First, the sample size was limited in this study, which might strict the statistical power of the association analysis. Second, except from individuals with extremely high HR, neither the early management nor secondary prevention guidelines recommendations for ischemic stroke include HR-controlling therapy.37,38 Third, more hemodynamic parameters (e.g., the product of HR and BP) need to be investigated in future studies. In addition, some residual confounders were not well adjusted in the study, such as inflammation, infection, and sedative medications.

These additional data should be fully collected in future studies. We performed a standard HR measurement following AHA scientific statement to minimize the effect of environmental factors. But the impact of emotional status (e.g., anxious, tense) on HR may not be completely avoided. Ultimately, the current analysis was not a prespecified study design. The results might be influenced by potential selection bias and confounding factors. Further studies are needed to validate the findings of this study.

## Conclusions

In this study, four HR trajectories are identified during acute phase of AIS by the latent mixture modeling. The sustained high HR trajectory pattern is associated with a higher risk of poor functional outcome than the markedly decreasing pattern in AIS patients, even when the HR is in the normal range. HR trajectory patterns demonstrate the utility of repeated HR measurements for outcome assessment. More attention should be paid to HR trajectory in stroke patients, especially those with sustained high HR. However, our results need to be validated in larger sample studies.

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### Conflicts of Interest

The authors report no disclosures relevant to the manuscript.

### Author Contributions

All authors were involved in the interpretation of study results and approval of the final version of the manuscript. Dr Wang Y contributed to the conception and design of the study. Dr Feng and Qin contributed...
to drafting the text. Dr Zhang contributed to statistical analysis and re-analysis in the revision. Dr Cheng and Liu contributed to the analysis and interpretation of data. Dr Wang A contributed to the statistical analysis. Dr Xu and Meng contributed to the acquisition of data. Dr Wang Y contributed to critical revisions of the manuscript. Dr Wang Y had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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