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Effect of renal function status on the prognostic value of heart rate in acute ischemic stroke patients

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ABSTRACT

Background and aims: The association between heart rate and prognosis of ischemic stroke remains debatable, and whether renal function status influences the relationship between them is still not elucidated.

Methods: A total of 3923 ischemic stroke patients were included in this prospective multicenter study from the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS). The primary outcome was a combination of death and major disability (modified Rankin Scale score $\geq$3) at 3 months after stroke. Secondary outcomes were, separately, death and major disability.

Results: The association between heart rate tertiles and primary outcome was appreciably modified by renal function status ($p_{interaction} = 0.037$). After multivariate adjustment, high heart rate was associated with increased risk of primary outcome in patients with abnormal renal function (odds ratio, 1.61; 95% confidence interval, 1.02–2.54; $p_{trend} = 0.039$) but not in patients with normal renal function (odds ratio, 0.96; 95% confidence interval, 0.75–1.23; $p_{trend} = 0.741$), when two extreme tertiles were compared. Each 10 bpm increase of heart rate was associated with 21% (95% CI: 1%–44%) increased risk of primary outcome, and a linear association between heart rate and risk of primary outcome was observed among patients with abnormal renal function (p for linearity = 0.002).

Conclusions: High heart rate may be merely a strong predictor of poor prognosis in acute ischemic stroke patients with abnormal renal function, suggesting that heart rate reduction should be applied to ischemic stroke patients with abnormal renal function to improve their prognosis.

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1. Introduction

Stroke is the leading cause of death and disabilities worldwide and leads to a huge economic burden on health care systems [1]. Numerous population-based studies have demonstrated that elevated heart rate (HR) is an independent predictor of cardiovascular mortality in the general population [2] and patients with cardiovascular diseases [3–5]. Moreover, the selective reduction of the heart rate with ivabradine has been a recognized therapeutic target in several cardiac conditions, such as ischemic heart disease and heart failure [5]. After an ischemic stroke, a faster HR was found to be associated with a worse functional outcome and more cognitive decline in patients [6,7]. In contrast, reports from some other studies found that HR was not associated with the morbidity or prognosis of stroke [8,9]. Whether the detrimental effect of elevated HR on prognosis could be modified by the existence of some particular conditions in the ischemic stroke patients remains unclear.

Patients with ischemic stroke often have abnormal renal function, chiefly characterized by reduced estimated glomerular filtration rate (eGFR), because of shared risk factors and pathophysiologic mechanisms affecting the kidney and brain [10]. Several population-based studies have found a significant association between HR and abnormal renal function [11,12]. Therefore, whether the association of HR with clinical outcomes is affected by renal function status because of a potential interaction between HR and renal function needs to be further elucidated. Additionally, previous studies found a J-shaped relationship between HR and mortality among patients with permanent atrial fibrillation or non-ST-segment elevation acute coronary syndromes [13,14]. However, the curve of relationship between HR and prognosis of ischemic stroke was never reported. The aim of this study is to investigate the pattern and magnitude of association between HR and prognosis of ischemic stroke according to the renal function status, based on a large prospective multicenter study of the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS).

2. Patients and methods

2.1. Study patients

This study was conducted on the basis of the CATIS, a randomized clinical trial carried out in 26 hospitals across China. Details on the design and major results of the CATIS trial have been reported previously [15]. Briefly, from August 2009 to May 2013, a total of 4071 patients aged over 22 years, who had first-ever ischemic stroke confirmed by computed tomography or magnetic resonance imaging of the brain within 48 h of symptom onset, and with an elevated systolic BP (SBP) between 140 and < 220 mmHg, were recruited. Patients with a SBP ≥220 or diastolic BP (DBP) ≥120 mmHg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension; those in a deep coma; and those treated with intravenous thrombolytic therapy were excluded. Further, 96 patients were excluded for missing baseline records of eGFR. After a 3-month follow-up, 52 patients were lost and the follow-up rate was 98.7%. Finally, a total of 3923 acute ischemic patients were included in this analysis. Almost all baseline characteristics of acute ischemic stroke patients were balanced between enrolled and excluded groups (Supplemental Table 1), indicating that those enrolled basically represented the total participants of CATIS.

The CATIS trial is registered at clinicaltrials.gov (Identifier: NCT01840072). This study was approved by the institutional review boards at Tulane University in the USA and Soochow University in China. Written consent was obtained from all study participants or their immediate family members.

2.2. Data collection

Demographic characteristics and lifestyles were collected at the time of enrollment. The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate stroke severity [16]. Ischemic stroke was classified as large artery atherosclerosis (thrombotic), cardiac embolism (embolic) and small artery occlusion lacunae (lacunar) [17]. Three BP measurements were obtained at baseline by trained nurses while the patient was in the supine position, using a standard mercury sphygmomanometer. Routine laboratory analyses (blood glucose, blood lipids, blood creatinine, etc.) were performed for all enrolled patients, in each participating hospital at admission.

2.3. Heart rate and renal function measurement

HR was recorded from an electrocardiogram monitor at the time of enrollment. Assessment of renal function was based on eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation with adjusted coefficient of 1.1 for the Chinese population [18]. According to the Kidney Disease: Improving Global Outcomes [19], we defined normal renal function as eGFR ≥90 mL/min per 1.73 m^2 and abnormal renal function as eGFR <90 mL/min per 1.73 m^2.

2.4. Outcome assessment

The primary outcome was death or major disability (modified Rankin Scale (mRS) score, 3–6) at 3 months after stroke. Secondary outcomes were separately those of death and major disability (mRS score of 6 and 3–5, respectively). We also included an ordered seven-level categorical score of the mRS at the 3-month follow-up visit as a secondary outcome for neurologic functional status based on a recommendation for acute stroke trials [20].

2.5. Statistical analysis

HR at baseline was categorized into three groups: <72, 72–77, and ≥78 bpm according to HR tertiles. Baseline characteristics were compared according to HR in both abnormal renal function and normal renal function groups. Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) of poor prognosis for upper tertiles, with the lowest tertile as the reference, among patients stratified by renal function, adjusting for age, sex, time from onset to hospitalization, antihypertensive treatment, current smoking, alcohol consumption, body mass index, dyslipidemia, blood glucose and SBP at baseline, ischemic stroke subtypes, and NIHSS score at baseline. To examine effect modification by renal function, we tested the statistical significance of HR category × renal function status on the primary outcome in multivariable logistic model by the likelihood ratio test. Sensitivity analyses were conducted to examine the association between HR and clinical outcomes based on diagnostic thresholds of eGFR for normal renal function, mild chronic kidney disease (CKD), and moderate CKD (≥90, 60–89, <60 mL/min per 1.73 m^2, respectively) [19].

Finally, we further used a logistic regression model with restricted cubic splines for HR to evaluate the pattern and magnitude of the association between HR and primary outcome, with the reference defined at 65 bpm and four knots placed at the 5th, 35th, 65th, and 95th percentiles of HR. Two-tailed $p < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using SAS statistical software (version 9.4, Cary, NC, USA).