Impact of Heart Rate Dynamics on Mortality in the Early Phase after Ischemic Stroke: A Prospective Observational Trial

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Background: Growing evidence suggests that the heart rate (HR) at rest is an independent predictor of cardiovascular mortality. In ischemic stroke, continuous monitoring of HR is the standard of care, but systematic data on its dynamics and prognostic value during the acute phase are limited. *Methods:* In this prospective observational study, HR was measured by continuous electrocardiographic monitoring on admission and during the first 72 hours of care among patients who were awake with ischemic stroke and survived until discharge. Functional outcome was assessed after 90 days. *Results:* Data from 702 consecutive patients were analyzed (median age, 73 years, 54% men). The time course of HR was initially characterized by a rapid decline during the first 12 hours after admission. Among patients who survived until day 90, this was followed by a continuous downward trend in HR, whereas death after discharge was associated with a secondary increase and a reversal point 12 hours after admission. After adjustment for established risk factors, this secondary increase during the acute period was an independent predictor of death (hazard ratio, 3.73; 95% confidence interval, 1.47-9.43; $P = .005$). *Conclusions:* A secondary rise of HR during care for acute ischemic stroke is an early sign of fatality and may represent a surrogate for an unfavorable sympathetic disinhibition. Further research is warranted to clarify the role of targeted HR reduction after ischemic stroke (http://clinicaltrials.gov/, unique identifier NCT01858779). **Key Words:** Stroke—heart rate—monitoring—ECG—stroke mortality.
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Introduction

Monitoring of the heart rate (HR) is a simple and generally accepted tool to guide the clinician during care for medical emergencies, critically ill patients, and acute cardiovascular and cerebrovascular diseases.[1] The physiological control of the HR is determined by intrinsic and extrinsic mechanisms, which predominantly act at the sinuatrial node via the sympathetic and parasympathetic nerve activities, circulating hormones, and autonomic reflex circuitries.[2] It promptly responds to changes in hemodynamic stability, metabolism, autonomic homeostasis and physical and mental activity during health and disease.[2,3] An elevated HR at rest was repeatedly found to be a predictor of mortality.[4-6] In addition, its pharmacologic reduction by ivabradine, a selective $I_{(f)}$ channel inhibitor, was able to reduce cardiovascular death and hospitalization in patients with heart failure.[7,8] HR during the subacute phase of stroke (measured within 120 days after the event) is associated with death and cognitive decline,[9] but systematic data on the very early period after stroke onset are limited.[10] As experimental data underline the importance

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of the HR during the first 72 hours after ischemic stroke,[11] we focused on this early period and investigated the HR dynamics during care at a monitored stroke unit and its impact on mortality after discharge.

Methods

Patients and Study Protocol

This study is part of a comprehensive clinical research program on the impact of continuous cardiac monitoring for patients with acute ischemic stroke (Stroke Arrhythmia Monitoring Database[12,13]). The protocol was approved by the local ethics committee of the Medical Faculty, University of Erlangen-Nuremberg, and registered with www.clinicaltrials.gov (NCT01177748). For this prospective observational trial on the HR (Stroke Arrhythmia Monitoring Database-HR), consecutive patients with acute cerebral ischemia within 72 hours after symptom onset were included during an 11-month period from May 2010 to March 2011. All patients were admitted to a 14-bed dedicated stroke unit of the Neurology Department, University Medical Centre, Erlangen, Germany. The diagnosis of cerebral ischemia was established according to the current guidelines[1] and in all cases confirmed by diagnostic imaging. In addition to the medical history and the findings from physical examination, the patients underwent a vascular diagnostic workup, including a 12-lead electrocardiogram on admission, ultrasound examination of the extracranial and intracranial vessels, echocardiography, and laboratory values (routine blood count, creatinine, troponin I, C-reactive protein (CRP), cholesterol levels, and hemoglobin A1c). Other procedures were performed as indicated by the clinician (eg, digital subtraction angiography, laboratory parameters indicative for thrombophilia, or autoimmune disease). Treatment at the stroke unit was offered to all patients for at least 72 hours and included a continuous monitoring of the electrocardiogram and the blood oxygen saturation and measurements of blood pressure, blood glucose levels, and body temperature in 4-hour intervals. The following patients were excluded from the analysis: (1) patients with hemorrhagic stroke on imaging, (2) patients in need of mechanical ventilation on admission or during the first 72 hours after admission, (3) patients who died within the first 72 hours after admission, (4) patients who discontinued treatment at the stroke unit before the completion of 72 hours, and (5) patients with cardiac pacemakers. The patients or their relatives were contacted for clinical outcome assessment on day 90 (range, 80-100) after stroke using a standardized telephone interview.

Measurement of HR

The ventricular rate was measured on admission to our emergency room and continuously during treatment at the stroke unit. For analysis, the HR was documented in 4-hour intervals. The patients were connected to a continuous multimodal monitoring system (Dräger; Infinity Series, Lübeck, Germany) including a 6-lead continuous electrocardiographic registration, which is displayed with 2 lines on a screen positioned at bedside and a second screen at a central control station. Before the measurements, the patients rested in a supine position with 45° elevation of the upper body, until a stable level of the HR was observed from the continuous electrocardiographic registration. The number (n) of QRS complexes within 15 seconds was counted, and the HR was calculated as $HR = 4 \times n$. In addition, the monitoring system is equipped with an automated HR feature, which uses the interval between consecutive R-waves for the calculation of the current HR. As this feature may be susceptible to artifacts, the conventionally measured values were used for the study. If a significant difference was observed in comparison with the automatically calculated values, the results from the conventional method were confirmed by repeated measurements.

Statistical Analysis

For statistical analysis, the SPSS Statistics software Version 20.0 (IBM, Armonk, NY) and the Office 2007 software (Microsoft Corp., Redmond, WA) were used. The Shapiro–Wilk and Kolmogorov–Smirnov tests were performed to test for normal distribution. Normally distributed data are reported by mean and standard deviation and compared using the Student t test. Other data were summarized by median and interquartile ranges, and the Mann–Whitney U test was used. The Pearson χ^2 test was applied to compare categorized variables. The level of significance was set a priori at P less than .05. To compare the HR during 72 hours of treatment, an analysis of variance with repeated measures was performed. The between-subject factor was membership to the group of survivors or deceased patients. To investigate the dynamics of the HR during treatment, values from the first day of treatment (8, 12, and 16 hours after admission) were compared with values of the third day (56, 60, and 64 hours after admission), whereas an increase more than 20% was defined as relevant. A univariate logistic regression analysis was calculated to identify parameters that were associated with death at day 90. Parameters that showed at least a trend in the univariate analysis ($P < .1$) were included into a multivariable logistic regression model to adjust for potential confounding factors.

Results

Clinical and Demographic Characteristics

A total of 702 patients (median age, 73 years; interquartile range, 62-80 years; 55.4% men) were included into the

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