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# Heart rate turbulence in acute ischemic stroke

**Helena Stengl[1,2,3], Ramanan Ganeshan[1,2], Regina von Rennenberg[1,2,4], Simon Hellwig[1,2,3], Juliane Herm[1,2], Thomas Krause[5], Axel Bauer[6], Matthias Endres[1,2,3,4,7,8], Karl Georg Haeusler[9*], Jan F Scheitz[1,2,3,4*] and Christian H Nolte[1,2,3,4*]**

## Abstract

**Background:** Heart rate turbulence (HRT), an ECG-based marker of autonomic cardiac regulation, has shown high prognostic value in patients with established cardiovascular diseases, while data in patients with acute ischemic stroke are scarce.

**Patients and methods:** The HRT parameters turbulence onset and turbulence slope were analyzed using Holter-ECG recordings from patients with acute ischemic stroke, consecutively enrolled in the prospective observational HEBRAS study. HRT was categorized as normal (category 0; both parameters normal), abnormal (category 1; one parameter abnormal), or severely abnormal (category 2; both parameters abnormal). Outcomes of interest were functional outcome according to modified Rankin Scale (mRS) score at 3 months, mortality at 1 year, newly detected atrial fibrillation (AF), and evidence of focal myocardial fibrosis on cardiovascular MRI.

**Results:** HRT was assessed in 335 patients in sinus rhythm (median age 69 years, 37% female, median NIHSS score 2 on admission), including 262 (78%) with normal HRT, 47 (14%) with abnormal and 26 (8%) with severely abnormal HRT. Compared with normal HRT, severely abnormal HRT was associated with increased disability [higher mRS] at 3 months (adjusted odds ratio [aOR]: 2.9, 95% confidence interval [CI]: 1.3–6.6), new AF (aOR: 3.5, 95% CI: 1.1–10.6), MRI-detected myocardial fibrosis (aOR: 5.8, 95% CI: 1.3–25.9), but not with mortality at 1 year after stroke (aOR: 3.0, 95% CI: 0.7–13.9). Abnormal HRT was not associated with the analyzed outcomes.

**Conclusions:** Severely abnormal HRT was associated with increased disability and previously unknown cardiac comorbidities. The potential role of HRT in selecting patients for extended AF monitoring and cardiac imaging should be further investigated.

## Keywords

Ischemic stroke, Stroke-Heart Syndrome, autonomic dysfunction, heart rate turbulence, Holter monitoring, atrial fibrillation, cardiovascular MRI

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[1]Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany
[2]Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin Berlin, Berlin, Germany
[3]Berlin Institute of Health (BIH) at Charité – Universitätsmedizin Berlin, Berlin, Germany
[4]German Center for Cardiovascular Research (DZHK), Partner Site, Berlin, Germany
[5]Department of Neurology, Jüdisches Krankenhaus Berlin, Berlin, Germany
[6]Working Group on Biosignal Analysis, Department of Cardiology, Medical University of Innsbruck, Innsbruck, Austria
[7]German Center for Neurodegenerative Diseases (DZNE), Partner Site, Berlin, Germany
[8]German Center for Mental Health (DZPG), Partner Site, Berlin, Germany
[9]Department of Neurology, Universitätsklinikum Würzburg (UKW), Würzburg, Germany

*These authors contributed equally to this work.

**Corresponding author:**
Helena Stengl, Klinik für Neurologie mit Experimenteller Neurologie, Charité-Universitätsmedizin Berlin, Hindenburgdamm 30, Berlin 12203, Germany.
Email: Helena.stengl@charite.de

## Introduction

The impact of the central autonomic system on cardiac complications after acute ischemic stroke is a focus of current research.[1–3] Multiple cardiac complications after stroke, such as elevated cardiac biomarkers, heart failure or severe arrhythmias are common, and several observational studies have shown an association with worse functional outcome and higher mortality.[2–6] There is growing evidence that stroke itself may alter autonomic cardiac regulation.[2,3] In addition, individuals with impaired autonomic cardiac regulation appear to be at higher risk for incident stroke.[7]

Non-invasive ECG-based markers provide an opportunity to investigate autonomic cardiac regulation, exerted via sympathetic and parasympathetic pathways.[7,8] Heart rate turbulence (HRT) – a marker of baroreflex sensitivity – is thought to reflect both sympathetic and parasympathetic autonomic cardiac regulation.[9,10] HRT refers to short, biphasic changes of sinus rhythm cycle-length following ventricular premature complexes (VPC). Simplified, in a premature ventricular ectopic heart beat the ventricular contraction is hemodynamically less efficient, resulting in a drop of blood pressure. In a healthy subject, this sudden drop of blood pressure after the VPC causes an abrupt loss of vagal activity, which leads to an immediate shortening of the first post-extrasystolic beat-to-beat intervals (i.e. a heart rate acceleration). The subsequent gradual increase of sympathetic activity and vascular resistance leads to a recovery of vagal activity, resulting in a gradual increase of beat-to-beat intervals (i.e. a heart rate deceleration).[9–12] These two phases of HRT are quantified by the parameters turbulence onset (TO) and turbulence slope (TS).

In patients with impaired autonomic cardiac regulation this physiologic process is compromised and abnormal HRT is associated with structural and functional cardiac disease.[9,12,13] Several studies have investigated HRT in populations with cardiac diseases such as myocardial infarction, heart failure or cardiomyopathies.[8,11,14] Especially in myocardial infarction and heart failure, abnormal HRT was found to be a reliable prognostic marker for mortality, severe arrhythmia, and new atrial fibrillation (AF).[11,14,15]

Given the correlation of HRT with altered cardiac structure and impaired function, abnormal HRT may indicate previously unknown heart disease in stroke patients. Thus, we aimed to investigate the frequency of abnormal HRT parameters in patients with acute ischemic stroke, and its association with clinical outcomes and previously unknown cardiac comorbidities.

## Methods

### Study design and study population

We analyzed data from the prospective, single-center, investigator-initiated, observational *HEart and BRain interfaces in Acute ischemic Stroke* (HEBRAS) study. The study was pre-registered (http://www.clinicaltrials.gov. Unique identifier: NCT02142413) and approved by the local Ethics Committee (EA2/033/14).

Hospitalized patients with acute ischemic stroke at the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, in Berlin, Germany were prospectively enrolled after providing written informed consent. A detailed study protocol and the main results have been published previously.[16,17] The aim of the HEBRAS study was to assess whether an intensified cardiac diagnostic work-up (including cardiovascular MRI (CMR) and prolonged Holter ECG recording) increases the yield of pathological findings with relevance for stroke etiology in cryptogenic stroke patients at enrollment compared with routine diagnostic care.

Patients with MRI-confirmed acute ischemic stroke were eligible for inclusion in the HEBRAS study within 6 days of stroke onset. To exclude patients with previously known possible sources of cardiac embolism and contraindications to undergo contrast enhanced CMR, the HEBRAS study protocol defined known AF, clinically severe heart failure (NYHA III-IV), and renal insufficiency (creatinine $>1.3$ mg/dl (females); creatinine $>1.7$ mg/dl (males)) as exclusion criteria.[16]

For the present post-hoc analysis of HRT parameters, 24-hour Holter recordings were used, in accordance with the consensus publication on HRT measurement.[9] In case of artifacts or measurement breaks, we pragmatically defined a required minimum duration of 10 h of analyzable recording time. In addition, patients were excluded if the Holter ECG started later than 5 days after symptom onset.

### Data collection and measurement of HRT

The CardioMem®4000 (GETEMED AG, Teltow, Germany) portable ECG recorder was used for Holter monitoring. Recording was started after enrollment in-hospital and continued for a maximum of 10 days. HRT analysis was conducted using the GETEMED software CardioDay V2.5. The first study-related 24-h recording was used for HRT measurement if the recording was sufficient for analysis. Otherwise, the study-related recording of the second day was analyzed.

Measurement and quantification of the HRT parameters TS and TO were conducted applying specific criteria recommended in a respective consensus paper.[9] TO and TS could be calculated from the average tachogram if the recording contained more than five VPCs meeting these criteria.[9] TO refers to the relative change of R-R intervals from before to after the ventricular premature complex (VPC) and the physiologic early acceleration of heart rhythm after the VCP typically leads to negative TO values (i.e. $<0\%$; see Figure 1). TS on the other hand quantifies the late deceleration phase after the VPC (for details regarding measurement criteria and calculation of TO and TS see supplementary methods online). According to the

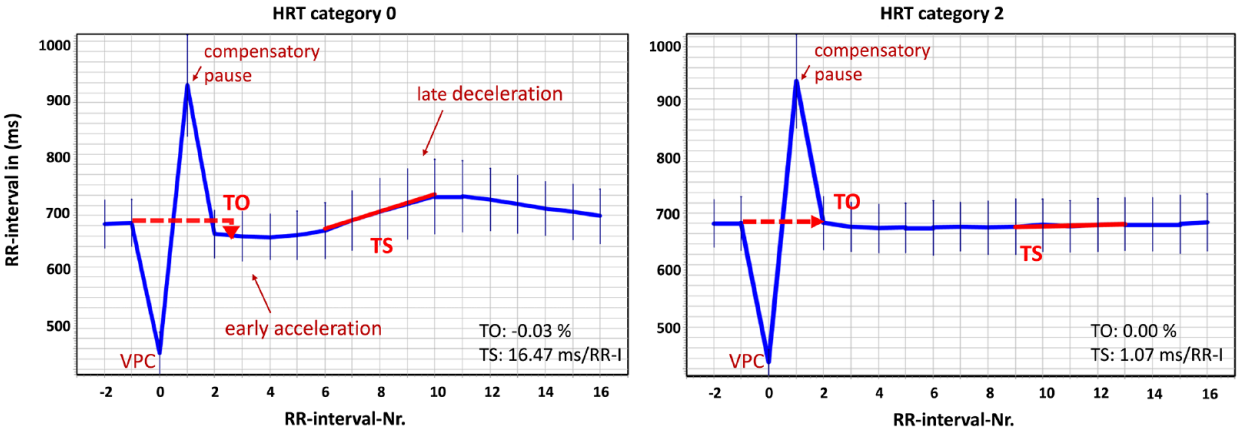


**Figure 1.** Example of a HRT tachogram with normal and severely abnormal HRT parameters. Left: Patient with HRT Category 0; normal turbulence onset (TO) and turbulence slope (TS). Right: Patient with HRT Category 2; abnormal TO and TS.

consensus statement on the interpretation of HRT, a TO $<0\%$ and TS $>2.5$ ms/R-R interval was considered normal.[9,10] Patients were divided into three categories:

- **Category 0:** TO and TS are normal, or the patient is in sinus rhythm, but has no or too few VPCs (i.e. ⩽5 VPCs) to calculate TO and TS.
- **Category 1**: TO or TS is abnormal.
- **Category 2**: Both, TO and TS are abnormal.

Categories are based on recommended standard of measurement.[9] As earlier risk stratification studies have shown that patients with few VPCs have low risk for cardiovascular events, we followed established recommendations and merged patients with ⩽5 VPCs with those having >5VPCs but normal TO and TS as category 0.[9,18,19]

## Outcomes

Cardiovascular outcomes and post-stroke functional status (modified Rankin Scale (mRS) score) were assessed by a standardized telephone interview at three and 12 months after the index stroke. If patients could not be reached, vital status was obtained from local registry offices.[16]

Outcomes of interest were (1) functional neurological status at 3 months, (2) all-cause mortality at 1 year, (3) first detection of cardiac comorbidities: (a) newly detected atrial fibrillation detection within 1 year, (b) cardiac fibrosis detected by late gadolinium enhancement (LGE) on cardiac MRI at baseline.

## Statistical analysis

Categorical data were reported as absolute and relative frequencies and continuous data as mean ± standard deviation (SD) or median with interquartile range [IQR], as appropriate. Categorical characteristics between the three HRT categories were compared using the $\chi^2$ test, and for continuous data using the Kruskal-Wallis test and one-way analysis of variance (ANOVA) for skewed and normally distributed variables, respectively. Odds ratios (OR) with 95% confidence intervals [CI] for each outcome of interest were calculated using unadjusted and adjusted models. Binomial logistic regression analyses were performed for bivariate outcomes and ordinal regression analysis for the endpoint functional outcome (mRS at 3 months). HRT status was entered as categorical variable with category 0 (normal HRT) as reference. Multiple adjustments were made based on established associated risk factors reported in the literature and variables associated with each outcome in univariable comparison with $p<0.1$. We limited the number of adjustment variables to avoid overfitting. The analysis examining the association between HRT and functional outcome was adjusted for age, history of hypertension, diabetes, myocardial infarction, previous stroke, and stroke severity on admission (as assessed by the National Institutes of Health's Stroke Scale (NIHSS)).[20] The analysis examining the association between HRT and mortality was adjusted for age, history of diabetes, and stroke severity (NIHSS score).[20,21] The analysis examining newly detected AF was adjusted for stroke severity and the $CHA_2DS_2$-VASc score. The $CHA_2DS_2$-VASc score is easily calculated, commonly used in clinical practice and has also been utilized for the prediction of AF in cryptogenic stroke although performance for predicting AF is only modest.[22,23] The analysis examining the association between HRT and focal myocardial fibrosis (presence of LGE on CMR) was adjusted for age, sex, hypertension, diabetes, and previous stroke. For the endpoint LGE on CMR, all patients with a known history of myocardial infarction were excluded before analysis to limit the results to patients with previously unknown myocardial fibrosis.

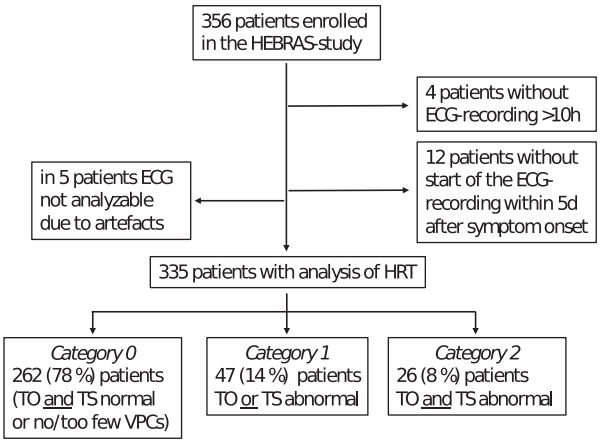


**Figure 2.** Flowchart of included patients.
ECG: electrocardiogram; TO: turbulence onset; TS: turbulence slope; VPC: ventricular premature complexes.

All tests were two-sided and $p$-values $< 0.05$ were considered statistically significant. No corrections were made for multiple comparisons. Statistical analyses were performed using IBM SPSS (SPSS, Inc., Chicago, IL, version 29.0).

## Results

### Baseline characteristics

Overall, 356 patients were enrolled in the HEBRAS study and underwent study-specific Holter ECG. After exclusion of patients with ECG recordings that were too short, too late, or of insufficient quality, 335 HEBRAS patients were eligible for the present HRT analysis (see Figure 2). Median age was 69 years [IQR 59.0–75.0] and 37% were female. Median NIHSS on hospital admission was two points [IQR 1–3] and 65 (19.4%) patients received intravenous thrombolysis. Median time from stroke onset to the start of study-specific Holter ECG was 50 h [IQR 31–71] and median duration of the HEBRAS Holter recordings overall was 162 h [IQR 103–210]. After subtracting sections with artifacts or breaks, a median recording duration of 23:20 h [IQR 22:02-24:00] was available for HRT assessment.

Of the 335 patients available for HRT analysis, 233 (69.6%) underwent the study-related contrast-enhanced CMR, including 212 (63.3%) patients without a history of myocardial infarction.

### Prevalence and characteristics of abnormal HRT values

HRT category was 0 (normal) in 262 (78.2%) of the 335 eligible patients. This included 128 patients with normal TO and TS values and 134 patients with ⩽5 VPC. HRT category was 1 (either TS or TO abnormal) in 47 (14%) patients. HRT category 2 (i.e. TS and TO abnormal) was found in 26 (7.8%) patients. Overall, TO was abnormal in 56 (16.7%) patients and TS in 43 (12.8%) patients. In univariate comparisons, age, prevalence of diabetes and hyperlipidemia, chronic obstructive pulmonary disease, history of myocardial infarction, and levels of cardiac biomarkers high-sensitivity troponin T and nt-pro-BNP differed between the three categories (see Table 1).

### HRT and clinical outcome

A total of 12 (3.6%) patients were lost to follow-up after 3 months and 26 (7.8%) patients after 12 months. Vital status information was available in 19 of these 26 patients (i.e. availability in 98% of the whole cohort). At 3 months after stroke, median mRS score was 1 [IQR 0–1] in the entire cohort and 1 [IQR 1–3] in the severely abnormal HRT group. Due to a relatively high rate of loss to follow-up at 1 year (7.8%), we restricted the further analysis regarding functional outcomes to the 3-month time point. At 1-year follow-up, 11 patients had died. Mortality rates were 2.3%, 4.4%, and 11.5% in HRT categories 0, 1, and 2, respectively (see Table 2). Within 1 year of the index stroke, 27/309 patients with follow-up experienced a recurrent stroke ($n = 18/243$ [7.4%], $n = 7/42$ [16.7%] and $n = 2/24$ [8.3%] in HRT category 0, 1, and 2, respectively; $p = 0.145$) and four patients a myocardial infarction.

In the adjusted ordinal regression analysis for functional outcome, HRT category 2 at baseline was associated with a shift in the distribution toward increased disability (adjusted OR 2.89, 95% CI: 1.27–6.59, $p = 0.01$) (see Figure 3).

In the unadjusted logistic regression analysis, HRT category 2 was associated with death at 1 year (OR 5.46, 95% CI: 1.28–23.27, $p = 0.02$). After adjustment for age, stroke severity (NIHSS), and history of diabetes, this association was no longer statistically significant (aOR 3.01, 95% CI: 0.65–13.92, $p = 0.16$). HRT category 1 was neither associated with functional outcome nor mortality (see Figure 4; for unadjusted OR see Supplemental Figure 1 online).

### HRT and detection of cardiac comorbidities

New AF was detected in 25 patients (7.5%). In 15 of these, AF was detected during in-hospital continuous ECG monitoring or study-specific prolonged Holter ECG and in 10 patients within 1 year after stroke in an outpatient setting.

CMR with contrast agent was performed in 233 patients. Myocardial fibrosis (LGE) was detected in 59/233 (25.3%) patients (see Table 2). 41/59 (69.5%) had no history of myocardial infarction. In 17 of these 41 (41.5%) cases LGE distribution corresponded to an ischemic and in 24 of 41 (58.5%) cases to a non-ischemic pattern. Frequency of newly detected myocardial fibrosis was 17%, 22%, and 56% in HRT categories 0, 1, and 2, respectively ($p$ for trend $p = 0.012$).

**Table 1.** Baseline characteristics of the entire cohort and HRT categories.

| | Total cohort | Category 0 (normal) | Category 1 (abnormal) | Category 2 (severely abnormal) | *p* |
|---|---|---|---|---|---|
| | *n* = 335 | *n* = 262 | *n* = 47 | *n* = 26 | |
| Age (years), median *[IQR]* | 69.0 [59.0–75.0] | 66.5 [57.0–73.25] | 74.0 [68.0–77.0] | 75.0 [68.5–78.0] | <0.001 |
| *Sex (female), n* (%) | 124 (37.0) | 95 (36.3) | 16 (34.0) | 13 (50.0) | 0.346 |
| Hypertension, *n* (%) | 198 (59.1) | 145 (55.3) | 31 (66.0) | 22 (84.6) | 0.09 |
| History of myocardial infarction, *n* (%) | 30 (9.0) | 16 (6.1) | 7 (14.9) | 7 (26.9) | 0.001 |
| Previous stroke, *n* (%) | 56 (16.7) | 43 (16.7) | 6 (12.8) | 7 (26.9) | 0.288 |
| Hyperlipidemia, *n* (%) | 117 (34.9) | 85 (32.4) | 16 (34.0) | 16 (61.5) | 0.012 |
| Diabetes mellitus | 60 (17.9) | 39 (15.0) | 12 (25.5) | 9 (34.6) | 0.015 |
| Congestive heart failure,[a] *n* (%) | 7 (2.1) | 5 (1.9) | 0 (0) | 2 (7.7) | 0.081 |
| Current smoker, *n* (%) | 89 (26.6) | 73 (27.9) | 13 (27.7) | 3 (11.5) | 0.196 |
| COPD, *n* (%) | 22 (6.6) | 13 (5.0) | 7 (14.9) | 2 (7.7) | 0.039 |
| Beta-blockers on admission, *n* (%) | 95 (28.4) | 69 (26.4) | 17 (36.2) | 9 (34.6) | 0.304 |
| Peak hs-cTnT ng/l, median [IQR] | 10 [6–16] | 8 [6–14] | 15 [9–20] | 17 [11–59] | <0.001 |
| Peak hs-cTnT [ng/l]>URL, *n* (%) | 106 (31.6) | 65 (24.8) | 25 (53.2) | 16 (61.5) | <0.001 |
| NTproBNP (ng/l),* | 124 [63–282] | 111 [52–255] | 132 [85–310] | 256 [164–1434] | <0.001 |
| Ejection fraction in CMR, %,** median [IQR] | 56.0 [48–62] | 56.0 [49–62] | 56.0 [46–64] | 56.0 [46–59] | 0.531 |
| i.v. thrombolysis, *n* (%) | 65 (19.4) | 44 (16.8) | 13 (27.7) | 8 (30.8) | 0.057 |
| Lesion side | | | | | |
| Left | 141 (42.1) | 103 (39.3) | 24 (51.1) | 14 (53.8) | 0.195 |
| Right | 146 (43.6) | 123 (46.9) | 16 (34.0) | 7 (26.9) | |
| Both sides | 48 (14.3) | 36 (13.7) | 7 (14.9) | 5 (19.2) | |
| Insular region affected | 37 (11.0) | 26 (9.9) | 7(14.9) | 4 (15.4) | 0.462 |
| NIHSS score at admission, median [IQR] | 2 [1–3] | 2 [1–3] | 2 [1–4] | 3 [1–5] | 0.134 |

*p*-Values for comparison between the three HRT categories. CMR: cardiovascular MRI, COPD: chronic obstructive pulmonary disease; IQR: interquartile range; hs-cTnT: high-sensitivity cardiac troponin T; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation; URL: upper reference limit.

[a]Patients with higher stage heart failure were not included in the study.

*Study-specific measurement after enrollment, available in *n* = 314 patients.

**Data available in 267 patients.

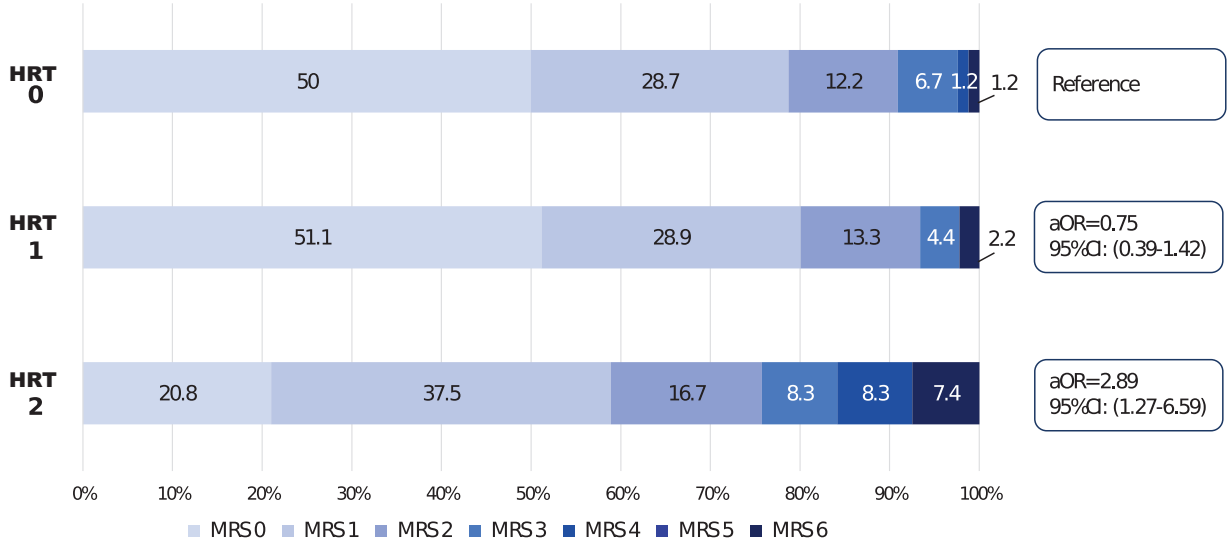


**Figure 3.** Functional outcome at 3 months after stroke with distribution of modified Rankin Scale (mRS) score in percent per HRT category. Adjusted Odds Ratio (aOR) with 95% Confidence Interval (CI) for HRT category 1 and 2 compared to category 0 respectively.

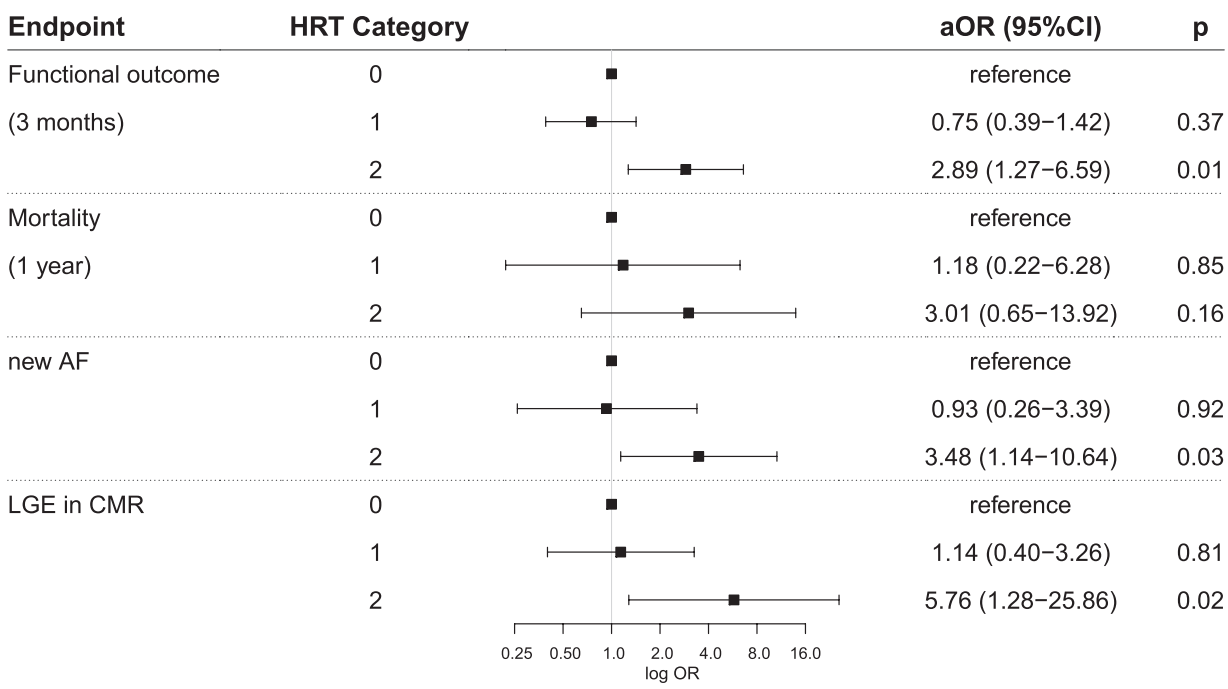


**Figure 4.** Association of HRT at baseline with shift toward an increased disability (functional outcome assessed using the modified Rankin Scale (mRS)) at 3 months after stroke, mortality at 1 year, AFDAS within 1 year and unknown myocardial fibrosis (LGE in CMR) at baseline. Analysis for unknown myocardial fibrosis was performed for the subgroup of patients with completed contrast-enhanced CMR without history of myocardial infarction.
AF: Atrial fibrillation; aOR: adjusted odds ratio; CI: confidence interval; CMR: cardiovascular MRI; LGE: Late Gadolinium Enhancement.

**Table 2.** Clinical outcomes and endpoints of interest for the entire cohort and per HRT category.

| Outcomes | | Total cohort | Category 0 (normal) | Category 1 (abnormal) | Category 2 (severely abnormal) | p |
|---|---|---|---|---|---|---|
| | *N* | *n* = 335 | *n* = 262 | *n* = 47 | *n* = 26 | |
| Clinical outcomes<br>mRS at 3 months, median [IQR] | 323 | 1 [0–1] | 1 [0–1] | 0 [0–1] | 1 [1–3] | 0.007 |
| Death at 1 year, *n* (%) | 328 | 11 (3.4) | 6 (2.3) | 2 (4.4) | 3 (11.5) | 0.042 |
| Cardiac findings | | | | | | |
| New atrial fibrillation, *n* (%) | 335 | 25 (7.5) | 16 (6.1) | 3 (6.4) | 6 (23.1) | 0.007 |
| Myocardial fibrosis (LGE) in CMR, *n*/*N* (%) | 233 | 59/233 (25.3) | 38/187 (20.3) | 12/33 (36.4) | 9/13 (69.2) | <0.001 |
| LGE in CMR in patients without known MI, *n*/*N* (%) | 212 | 41/212 (19.3) | 30/176 (17) | 6/27 (22.2) | 5/9 (55.6) | 0.016 |

*p*-values for comparison between the three HRT categories. AF detection within 1 year after stroke, CMR: cardiovascular MRI; LGE: late gadolinium enhancement; MI: myocardial infarction; *N*: number of patients with available data.

Logistic regression analysis showed a statistically significant association of HRT category 2 with both new AF (aOR: 3.48, 95% CI: 1.14–10.64, $p = 0.03$), and unknown myocardial fibrosis (aOR: 5.76, 95% CI: 1.28–25.86, $p = 0.02$, see Figure 4). HRT category 1 was not associated with new AF or unknown myocardial fibrosis.

## Discussion

The post-hoc analysis of the prospective, observational HEBRAS study yielded three main findings. First, one in twelve patients had a severely abnormal HRT according to baseline Holter ECG recording. Second, patients with severely abnormal HRT were more likely to have increased disability at 3 months compared to patients with normal HRT. Third, severely abnormal HRT was associated with previously unknown cardiac comorbidities, namely a threefold higher detection rate of new AF during 1 year of follow-up and a fivefold higher detection rate of focal myocardial fibrosis in the subgroup of study patients undergoing CMR.

HRT has been extensively studied in other populations with prevalent cardiovascular disease but little is known

about the role of HRT in acute ischemic stroke.[8,11,24] In a previous study analyzing HRT in acute ischemic stroke patients and control subjects, reported prevalence of HRT category 1 and 2 (43% and 24%, respectively) in stroke patients were higher than in our cohort.[24] However, differences in HRT categorization and patients' comorbidities need to be considered. In a meta-analysis, Disertori et al., reported that the frequency of severely abnormal HRT (category 2) in patients with heart failure was 20% to 29% in the investigated populations.[14] Abnormal HRT was reported to be more common in the presence of reduced left ventricular ejection fraction and structural heart disease.[9,12,13] Frequency of HRT category 2 in this cohort of patients with mild-to moderate stroke was 8%, which is within the reported range of 4% to 28% found in patients with acute myocardial infarction.[14]

Differences in age, prevalence of diabetes, hyperlipidemia and COPD between HRT categories in our cohort of stroke patients were consistent with previous studies in non-neurological cohorts.[11,25,26] We also found no relevant sex differences.[9,27]

In this analysis we investigated the association of HRT with clinical outcomes in stroke patients. In populations with cardiovascular disease, mainly myocardial infarction and heart failure, HRT has been strongly associated with cardiac death and incident cardiac arrhythmias.[11,14] In the present cohort, functional outcome 3 months after stroke was worse in patients with HRT category 2 when compared to patients with normal HRT. This finding is corroborated by several studies investigating the autonomic marker heart rate variability (HRV) in stroke, which found an association between reduced HRV and worse functional outcome.[28,29] However, compared to HRV, which primarily represents vagal cardiac control, HRT is thought to reflect both parasympathetic and sympathetic cardiac regulation.[30] HRT may be more sensitive to detect disturbances in autonomic cardiac control after stroke, as sympathetic overactivation has been discussed as a key mechanism leading to cardiac involvement after stroke.[2,3] Notably, HRT category 1 – in contrast to HRT category 2 – did not correlate with the outcomes of interest examined in this analysis. We hypothesize that the difference in both categories regarding the association with the analyzed outcomes are mainly driven by more severe known and unknown cardiac comorbidities and cardiovascular risk factors. As many previous risk stratification studies showed a strong predictive value for HRT category 2, but not for HRT category 1, there seems to be a relevant difference regarding the extent of autonomic impairment between both categories.[8,14,31] In addition, possible neurocardiogenic mechanism might be discussed.[2] Candemir and Onder found an association between abnormal HRT and right hemispheric lesions.[24] However, even though a slightly higher stroke severity according to the NIHSS was observed in patients with severely abnormal HRT, we did not find strong evidence of a neurogenic mechanism taking stroke lesion side and affection of the insular cortex – as part of the central autonomic nervous system – into account.

Since an association of abnormal HRT parameters with newly detected atrial fibrillation has been described in cohorts with myocardial infarction, we aimed at investigating this association in stroke patients.[15,27] As atrial fibrillation is considered a major risk factor for stroke and its detection is essential for secondary prevention, our findings support the hypothesis that HRT at baseline may be a useful tool to identify patients with acute ischemic stroke who may benefit from intensified cardiac monitoring.[32]

In our stroke cohort, abnormal TS and TO showed an association with unknown focal myocardial fibrosis detected by CMR at baseline, consistent with the known association between structural heart disease and abnormal HRT.[11,13] The association persisted after adjustment for conventional cardiovascular risk factors. A thorough diagnostic cardiac work-up after stroke is essential to investigate stroke etiology but may also help detecting preexisting – clinically silent – cardiac disease after stroke.[3,4] As advanced cardiac imaging modalities such as CMR are not available for the majority of patients with acute ischemic stroke at present, HRT status may help to pre-select stroke patients who may have pathological findings. However, future studies are needed to demonstrate a potential benefit of CMR-detected fibrosis (for both ischemic- and non-ischemic pattern) in asymptomatic stroke patients.

Strengths of this post hoc analysis include the prospective data collection and the highly standardized assessment of Holter ECG monitoring and CMR. The following limitations must be considered. First, measurement of HRT in acute ischemic stroke has not been established so far. Therefore, we applied the recommended cut-offs for abnormal HRT parameters based on established consensus recommendations for cardiovascular populations.[9] Second, the number of stroke patients with severely abnormal HRT was small and mortality rate was low which reduced statistical power. Further studies with longer follow-up periods or larger sample sizes may be necessary to evaluate the full prognostic potential of HRT with respect to stroke mortality. Third, we did not validate HRT classification in multiple Holter ECG recordings from the same patients. Fourth, median time from onset of stroke symptoms to start of Holter ECG was 54.5 h. Very early (and transient) abnormalities after stroke may have been missed. Fifth, given the necessity of written informed consent and ability to undergo CMR, this stroke cohort included patients with mild to moderate stroke and therefore the results cannot be generalized to all stroke patients. In addition, patients with more severe strokes and larger infarcts may be better suited to analyze the effect of lesion size on HRT, which we did not provide in this study. Sixth, loss to follow up rates after 1 year was 8% for any event and functional outcome and 2% for vital status. Therefore, we limited the analysis

regarding functional outcome to the 3 months follow up. Finally, the exclusion of stroke patients with severe heart failure and severely impaired renal function may have resulted in lower rates of abnormal HRT in this cohort.

## Conclusion

In this cohort of prospectively enrolled patients with mild-to-moderate acute ischemic stroke, abnormal HRT was found in one out of seven patients, and severely abnormal HRT in one out of twelve patients.

Severely abnormal HRT was associated with increased disability on mRS score 3 months after stroke, newly detected AF within 1 year after stroke, and cardiac fibrosis on CMR at baseline. Future studies should further evaluate the potential of HRT as a screening tool for cardiac comorbidities in stroke and for preselection for extended atrial fibrillation monitoring and advanced cardiac imaging. Given the widespread availability of routine monitor ECG measurements in stroke unit care, HRT may be a useful tool for investigating cardiac autonomic regulation in the early phase after stroke.

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### Ethical approval

The study was approved by the local ethics committee of Charité-Universitätsmedizin Berlin (EA2/033/14).

### Informed consent

All patients included in the HEBRAS study provided written informed consent.

### Guarantor

JFS

### Contributorship

CHN and KGH conceived the HEBRAS study. JFS, HS, KGH, and CHN designed the present substudy. CHN, KGH, SH, TK and JH acquired the data. HS, RG, JFS, CHN, and KGH conducted the analysis and interpretation of the data. HS wrote the first draft of the manuscript. All authors participated in revising and editing the paper and provided final approval.

### ORCID iDs

Helena Stengl https://orcid.org/0000-0002-9270-7665
Jan F Scheitz https://orcid.org/0000-0001-5835-4627
Christian H Nolte https://orcid.org/0000-0001-5577-1775

### Supplemental material

Supplemental material for this article is available online.

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