Journal of the American Heart Association

ORIGINAL RESEARCH

Effect of Heart Rate Variabilities on Outcome After Acute Intracerebral Hemorrhage: A Post Hoc Analysis of ATACH-2

Kaori Miwa, MD, PhD; Masatoshi Koga, MD, PhD; Mayumi Fukuda-Doi, MD, MPH, PhD; Haruko Yamamoto, MD, PhD; Kanata Tanaka, MD, PhD; Sohei Yoshimura, MD, PhD; Masafumi Ihara, MD, PhD; Adnan I. Qureshi, MD, PhD; Kazunori Toyoda, MD, PhD

BACKGROUND: To explore how the clinical impact of heart rate (HR) and heart rate variabilities (HRV) during the initial 24 hours after acute intracerebral hemorrhage (ICH) contribute to worse clinical outcomes.

METHODS AND RESULTS: In the ATACH-2 (Antihypertensive Treatment in Intracerebral Hemorrhage 2) trial, the HR was recorded for every 15 minutes from baseline to 1 hour and hourly during the initial 24 hours post-randomization. We calculated the following: mean, standard deviation, coefficient of variation, successive variation, and average real variability (ARV). Outcomes were hematoma expansion at 24 hours and unfavorable functional outcome, defined as modified Rankin Scale score 4 to 6 at 90 days. Of the 1000 subjects in ATACH-2, 994 with available HR data were included in the analyses. Overall, 262 experienced hematoma expansion, and 362 had unfavorable outcomes. Increased mean HR was linearly associated with unfavorable outcome (per 10 bpm increase adjusted odds ratio [aOR], 1.31, 95% CI, 1.14–1.50) but not with hematoma expansion, while HR-ARV was associated with hematoma expansion (aOR, 1.06, 95% CI, 1.01–1.12) and unfavorable outcome (aOR, 1.07, 95% CI, 1.01–1.3). Every 10-bpm increase in mean HR increased the probability of unfavorable outcome by 4.3%, while every 1 increase in HR-ARV increased the probability of hematoma expansion by 1.1% and unfavorable outcome by 1.3%.

CONCLUSIONS: Increased mean HR and HR-ARV within the initial 24 hours were independently associated with unfavorable outcome in acute ICH. Moreover, HR-ARV was associated with hematoma expansion at 24 hours. This may have future therapeutic implications to accommodate HR and HRV in acute ICH.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT01176565.

Key Words: heart rate ■ heart rate variabilities ■ intracerebral hemorrhage ■ randomized controlled trial ■ stroke

Spontaneous intracerebral hemorrhage (ICH) accounts for 15% to 20% of all stroke, yet it causes a disproportionately high mortality and has limited treatment options.[1] Achieving early blood pressure control has been the focus of intensive therapeutic investigation.[2] Meanwhile, heart rate (HR) is a known and well-studied risk factor for adverse outcomes in the setting of cardiac diseases.[3] Increased absolute HR reflects stress conditions related to acute stroke and is associated with unfavorable outcome.[4–6] However, the extent of its prognostic power and strategic value for patients with

Correspondence to: Kaori Miwa, MD, PhD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan. E-mail: miwa@osaka-njm.net; miwak@ncvc.go.jp

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.020364

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Higher heart rate (HR) and impaired HR variabilities in the setting of acute stroke reflect not only various stress conditions but also post-stroke cardiosympathetic-vagal dysregulations; however, its prognostic values for patients with acute intracerebral hemorrhage remain unclear.
- HR average real variability within 24 hours after intracerebral hemorrhage had a consistent association with hematoma expansion at 24 hours and functional 3-month outcomes.
- In addition, increased mean HR was linearly associated with subsequent functional disability.

What Are the Clinical Implications?

- HR average real variability could represent more physiologically relevant HR variation attributable to concomitant autonomic dysfunction.
- It would be important to ensure that HR control is smooth and sustained in the hyperacute phase of intracerebral hemorrhage.
- Future studies are expected to investigate the clinical implications and optimal HR management strategies in the acute period of intracerebral hemorrhage.

Nonstandard Abbreviations and Acronyms

ARV	average real variability
ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale

acute stroke remains unclear. Possibly, the effect of brain-heart interaction, such as cardiosympathetic-vagal dysregulation, which reflects the post-stroke dysregulation of the autonomic nervous system with excess sympathetic activity, would affect the cardiac ability to accommodate instantaneously according to circulatory changes.[7] Consequently, the discordant HR fluctuation is manifested as impaired HR variabilities (HRV).[7] Impaired HRV has been shown to be an independent predictor of mortality not only in the general population but also in patients with cardiac diseases.[8,9] To date, however, studies investigating the association between clinical outcomes after stroke and whole spectrum of HR measures are scarce, leaving limited elucidation of the impact of HRV, particularly in patients on acute treatment for ICH. The overarching hypothesis was that impaired HRV in acute ICH would have a clinical impact on hematoma expansion at 24 hours and functional outcome at 3 months. We therefore performed an exploratory analysis of the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage) trial data focusing on patients with acute ICH.

METHODS

Study Design and Inclusion Criteria

The whole data set of ATACH-2 is currently open to the public and is available upon request to the National Institute of Neurological Disorders and Stroke. We conducted a post hoc analysis of the ATACH-2 trial, an international, randomized, open-label trial to determine the efficacy of rapidly lowering systolic blood pressure in patients with acute supratentorial ICH within 4.5 hours of onset of <60 mL who also had elevated systolic BP (>180 mm Hg), the details of which have been described elsewhere.[10] Participants were randomized to intensive treatment (target systolic BP, 110–139 mm Hg within 2 hours) or standard treatment (target systolic BP, 140–179 mm Hg within 2 hours) using intravenous nicardipine.

Standard Protocol Approvals, Registrations, and Patient Consents

The ATACH-2 study is registered with ClinicalTrials.gov (NCT01176565) and the University Hospital Medical Information Network clinical trial registry in Japan (UMIN 000006526), approved by ethical committees/competent authorities in all participating sites. Informed consent was obtained from each subject, her/his legally authorized representative, or a relative.

Heart Rate Monitoring and Heart Rate Parameters

The ATACH-2 trial recorded the maximum and minimum HR for every 15 minutes for the first hour after randomization and every hour thereafter between 1 and 24 hours in the acute period (27 measurements altogether).[10] We focused on the maximum HR because prior studies showed that higher HR has clinical impact on functional outcomes and mortality.[4,11] We calculated 5 HR measures: mean, SD, coefficient of variation (defined as SD/mean×100%), successive variation, and average real variability (ARV) during the initial 24-hour post-randomization. Successive variation is the average squared difference between the consecutive order of individual measurements $\left(\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}|x_{i+1}-x_i|^2}\right)$.

ARV is calculated as the average absolute difference between the consecutive order of individual HR measurements $\left(\frac{1}{n-1}\sum_{i=1}^{n-1}|x_{i+1}-x_i|\right)$.

Clinical Outcomes

Following the criteria used in ATACH-2,[10] the predefined outcome was unfavorable functional outcome, defined as a modified Rankin Scale (mRS) score of 4 to 6, at 90 days after randomization. Moreover, hematoma expansion, which is a neuroimaging marker of primary brain injury and a factor associated with unfavorable outcome, was defined as >33% or >6 mL increase[12] in volume on the computed tomographic scan obtained at 24 hours compared with the baseline scan, or surgical evacuation of hematoma within 24 hour regardless of post-surgery hematoma volume.

Statistical Analysis

The demographic and baseline characteristics of the study subjects were summarized as mean±SD for continuous variables, number of patients (%) for categorical variables, and median with interquartile range for ordinal variables, as appropriate. We tested for differences with Student t test for continuous variables, chi-square test for binary variables, and the Wilcoxon Rank-sum test for ordinal variables. There were no significant differences in hematoma expansion and unfavorable outcome between randomized treatment groups,[10] thus we combined both groups into a single cohort to assess the association between HR parameters and clinical outcomes for the present analyses. We used single imputation for missing HR measurements using regression analyses. We modelled each HR measure as continuous variables and also categorized those into quartile groups. The multivariable analysis was adjusted for the established predictors of outcome: age, sex, prior antihypertensive medication, initial National Institutes of Health Stroke Scale (NIHSS), hematoma location (lobar versus nonlobar) at baseline, hematoma volume at baseline, and systolic blood pressure at presentation in the emergency department. Our model was also adjusted for the treatment allocation and mean maximum dose of nicardipine. Multivariable analysis was performed separately for each HR measure. Models are evaluated using the Akaike Information Criterion (AIC), where smaller values indicate better model fit. Testing for interaction was used to determine heterogeneity in the associations of HR measures with outcomes between the treatment groups. We further tested margin plot analyses along with a quadratic term, only if the significant associations appeared in the logistic regression model. We also performed restricted cubic spline analyses with 3-knots to flexibly display the relationship between HR measures and clinical outcomes.

All *P* values were two sided, and a *P* value of <0.05 was considered statistically significant. Analysis was performed using STATA (version 16, StataCorp LP, College Station, TX).

RESULTS

The baseline characteristics of the study group were previously described.[10] Among 1000 patients enrolled in ATACH-2, baseline HR data were available for 998 participants. For the entire cohort, patients who died within the initial 24 hours (n=4) were excluded, leaving 994 patients for further investigation (Table 1). Of these, there were missing data for 43 patients with hematoma expansion and 38 with unfavorable outcomes at 90 days, respectively. Altogether, 262 (27%) patients experienced hematoma expansion and 362 (37%) had unfavorable outcomes at 90 days (mRS 4–6), including death (mRS 6) in 63 (6.6%).

Table 1. Baseline Characteristics

Variable	All (n=994)
Age, y	62 [52–71]
Male	615 (62)
Asian	534 (54)
Hypertension	788 (79)
Premorbid antihypertensive medication, (n=987)	490 (50)
SBP at initial presentation, mm Hg	200±27
DBP at initial presentation, mm Hg	111±20
Prior stroke	164 (16)
Atrial fibrillation, (n=984)	35 (3.5)
Ischemic heart disease	43 (4.3)
Dyslipidemia	240 (24)
Baseline NIHSS score	11 [6–16]
Baseline Glasgow coma score	15 [13–15]
Lobar ICH	116 (11)
Left-sided ICH	519 (52)
ICH volume, mL	10.2 [5.1–18.4]
Intensive SBP control randomization arm	495 (50)
Mean maximum nicardipine infusion rate, mg/h	3.7 [1.7–6.9]
Hydrocephalus, (n=985)	132 (13)
Evacuation surgery	44 (4.4)
Mean HR, median [IQR], (range), bpm	86 [77–96], (53–134)
HR-SD, bpm	8.9 [6.8–11.4]
HR-CV, %	10.3 [7.9–13.3]
HR-SV, bpm	8.5 [6.2–11.3]
HR-ARV, bpm	6.2 [4.6–8.2]

Values are presented as frequencies (percentages), means±SD, or median [interquartile ranges], as appropriate. ARV indicates average real variability; CV, coefficient of variation; DBP, diastolic blood pressure; HR, heart rate; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; and SV, successive variation.

The study population included 26838 HR measurements (ie, 994×27) of 994 subjects at 24 hours intervals. Of these, we imputed 570 HR measurements (2%). The median values of mean HR within 24 hours after ICH were 86 (IQR: 77–96, range: 53–134) bpm. The median values of mean HR for the first 24 hours after randomization according to the treatment group are shown in Figure S1. The median value of HR-ARV was 6.2 (IQR: 4.6–8.2) bpm. There was no significant difference in the value between mean HR, HR-ARV and treatment allocations (Table S1).

Heart Rate Variabilities and Hematoma Expansion

Among the HR measures, only HR-ARV was modestly associated with hematoma expansion in multivariable analysis (odds ratio [OR] 1.06; 95% CI 1.01–1.12, *P*=0.029) (Table 2). The adjusted model minimized the AIC (unadjusted model: 951, adjusted model: 935, ΔAIC=−26). HR-ARV had a significant association with hematoma expansion (the highest quartile of HR-ARV, adjusted OR 1.64; 95% CI 1.07–2.51; *P* trend =0.016; Figure 1A). The adjusted restricted cubic spline model shows that higher HR-ARV was associated with a linear rise in the risk of hematoma expansion (Figure 2A). The probability of hematoma expansion increased from 24% at 4 of HR-ARV to 33% at 12 of HR-ARV, resulting in a 1.1% increased probability of hematoma expansion per 1 increase in HR-ARV (Figure 2B). There was no significant interaction between HR-ARV and treatment allocation (*P*=0.591).

Heart Rate and Unfavorable Functional Outcome

Increasing mean HR (per 10 bpm) was significantly associated with unfavorable functional outcome in the fully adjusted model (OR 1.31; 95% CI 1.14–1.50, *P*<0.001) (Table 3). The adjusted model minimized the AIC (unadjusted model: 1143, adjusted model: 812, ΔAIC=−331). The quartiles of mean HR were associated with the outcome in a linear fashion (the highest quartile of mean HR; OR 2.81; 95% CI 1.73–4.58, *P*<0.001) (Figure 1B). The adjusted restricted cubic spline model shows that higher mean HR associated with a linear rise in the risk of unfavorable outcome (Figure 3A). The probability of unfavorable functional outcome increased from 22% at 60 bpm of mean HR to 48% at 120 bpm of mean HR, resulting in a 4.3% increased probability of worse functional outcome per 10-bpm increase in mean HR (*P*=0.001) (Figure 3B). There was no significant interaction between mean HR and treatment allocation (*P*=0.82).

Heart Rate Variabilities and Unfavorable Functional Outcome

HR-ARV were independently associated with unfavorable outcome in the fully adjusted model (OR 1.07; 95% CI 1.01–1.13, *P*=0.023) (Table 3). The adjusted model minimized the AIC (unadjusted model: 1158, adjusted model: 824, ΔAIC=−334). HR-ARV had a significant association with unfavorable outcome (the highest quartile of HR-ARV; adjusted OR 1.75; 95% CI 1.09–2.83; *P* trend=0.016; Figure 1B). The adjusted restricted cubic spline model shows that higher HR-ARV was associated with a linear rise in the risk of unfavorable outcome (Figure 4A). The probability of unfavorable functional outcome increased from 35% at 6 of HR-ARV to 43% at 12 of HR-ARV, resulting in a 1.3% increased probability of worse functional outcome per 1 increase in HR-ARV (Figure 4B). There was a marginal effect modification between HR-ARV and treatment allocation for the risk of unfavorable functional outcome (*P*=0.10). In the intensive treatment arm, the probability of worse functional outcome increased from 32% at 6 of HR-ARV to 36% at 12 of HR-ARV, resulting in a 0.6% increased probability of

Table 2. Logistic Regression Models Showing the Effect of Heart Rate Parameter Predictors on the Odds Ratio of Hematoma Expansion at 24 Hours

	Unadjusted			Adjusted		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Mean HR, per 10 bpm	1.01	0.99–1.16	0.275	1.05	0.93–1.18	0.434
HR-SD	1.02	0.98–1.05	0.337	1.01	0.97–1.05	0.464
HR-CV	1.00	0.97–1.04	0.535	1.00	0.97–1.04	0.656
HR-SV	1.04	1.00–1.07	0.042*	1.03	0.99–1.07	0.126
HR-ARV	1.06	1.01–1.12	0.012*	1.06	1.01–1.12	0.029*

Adjusted for age, sex, treatment arm, baseline NIHSS, premorbid antihypertensive medication, location of ICH, mean max nicardipine, SBP at presentation in emergency department, ICH volume, and atrial fibrillation. ARV indicates average real variability; bpm, beats per minute; CV, coefficient of variation; HR, heart rate; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variability.

*$P<0.05$.

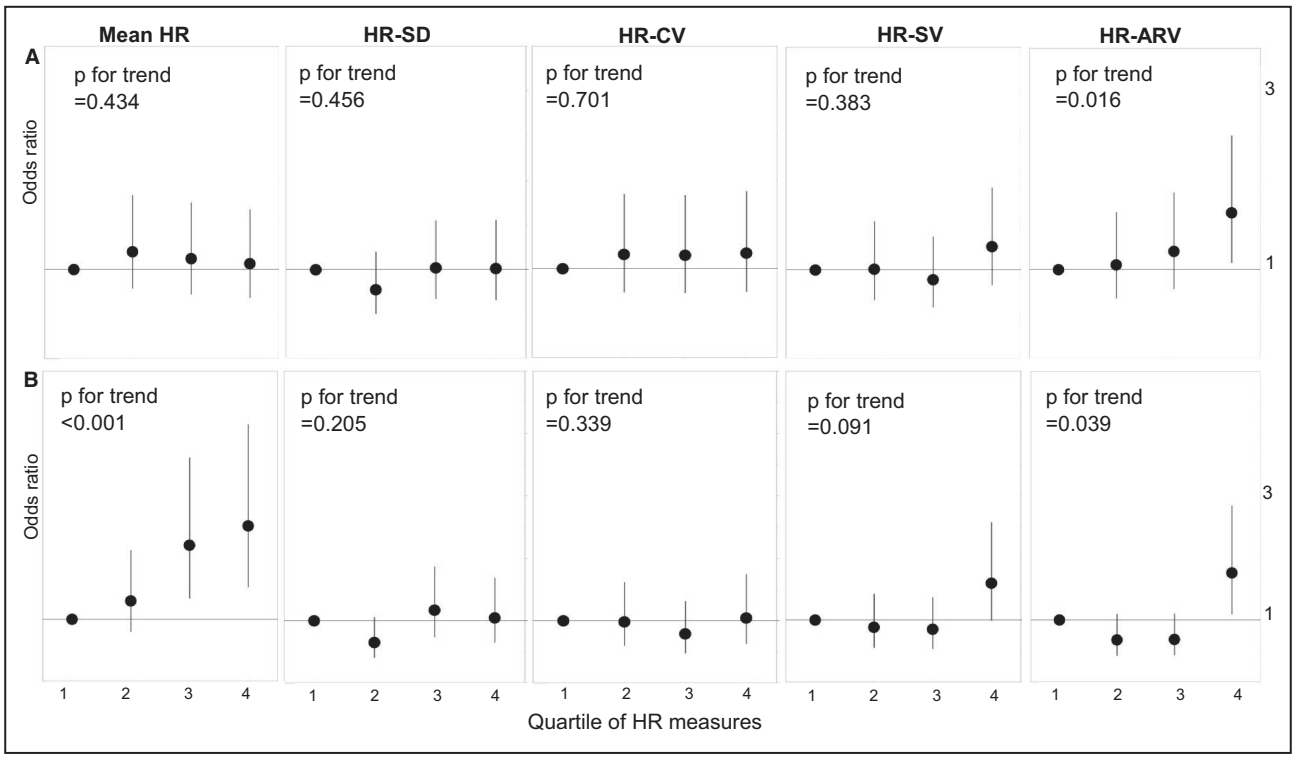


Figure 1. The odds ratio according to quartiles of heart rate (HR) measures.
A, for hematoma expansion at 24 hours; (**B**) for unfavorable functional outcome at 90 days. Lowest quintile is reference. ARV indicates average real variability; CV, coefficient of variation; and SV, successive variation.

worse functional outcome per 1 increase in HR-ARV. Whereas in the standard treatment, the probability of outcome increased from 39.2% at 6 of HR-ARV to 52.6% at 12 of HR-ARV, resulting in a 2.2% increased probability of worse functional outcome per 1 increase in HR-ARV (Figure 4C).

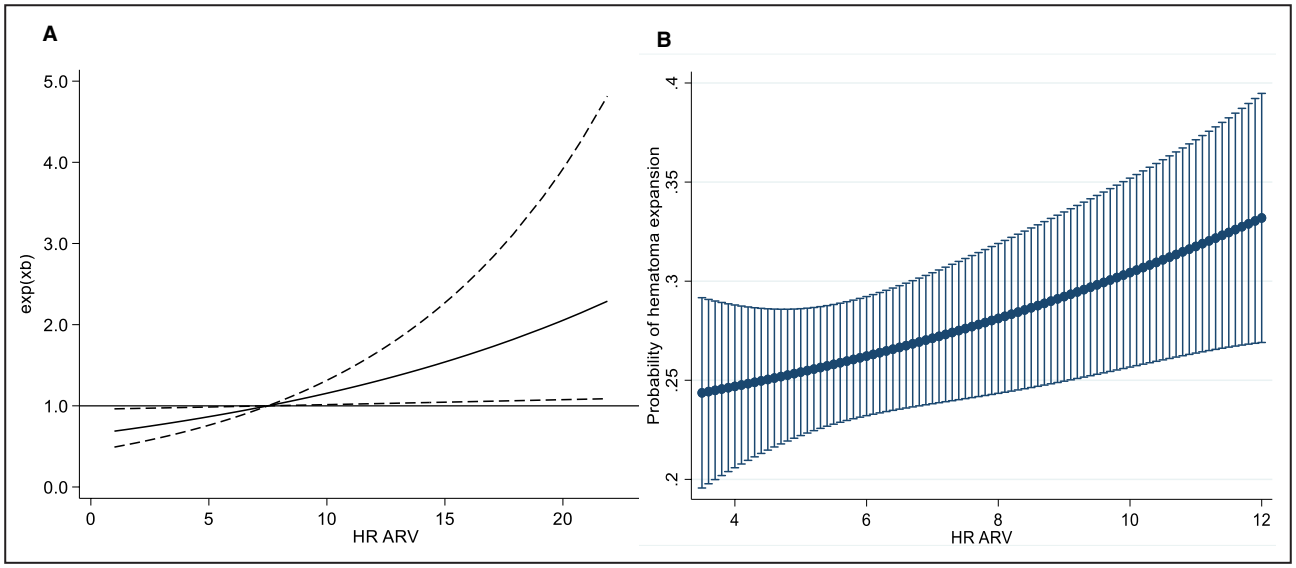


Figure 2. Associations between heart rate-average real variability (HR-ARV) and hematoma expansion at 24 hours.
A, The adjusted cubic spline model. This curve (black line) displays that higher HR-ARV appears to be associated with a rise in the risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1. **B**, Probability of hematoma expansion with margins plot, including 95% CIs. Every 1 increase in HR-ARV is associated with an absolute increase in the probability of hematoma expansion by 1.1%.

Table 3. Logistic Regression Models Showing the Effect of Heart Rate Parameter Predictors on the Odds Ratio of Unfavorable Functional Outcome (mRS4–6 at 90 Days)

	Unadjusted			Adjusted		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Mean HR, per 10 bpm	1.24	1.12–1.37	<0.001*	1.31	1.14–1.50	<0.001*
HR-SD	1.01	0.98–1.05	0.428	1.01	0.97–1.06	0.515
HR-CV	0.98	0.98–1.02	0.318	0.98	0.94–1.02	0.211
HR-SV	1.05	1.01–1.08	0.03†	1.04	0.99–1.09	0.063
HR-ARV	1.07	1.03–1.13	0.001†	1.07	1.01–1.13	0.023†

Adjusted for age, sex, treatment arm, baseline NIHSS, premorbid antihypertensive medication, location of ICH, mean max nicardipine, SBP at presentation in emergency department, ICH volume, and atrial fibrillation. ARV indicates average real variability; bpm, beats per minute; CV, coefficient of variation; HR, heart rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; and SV, successive variability.

*$P<0.01$.

†$P<0.05$.

For the separate components of the functional outcome, HR and HR fluctuations were not associated with death at 90 days (mRS 6) in the fully adjusted model (data not shown).

DISCUSSION

In the post hoc analysis of the ATACH-2 trial, a major finding is that increased mean HR and HR-ARV within 24 hours after ICH are associated with subsequent functional disability. HR-ARV had a consistent association with hematoma expansion at 24 hours and functional 3-month outcomes. We found evidence for effect modification according to the treatment group, such that the association of HR-ARV with worse functional outcome remained significant. In contrast, mean HR within 24 hours after ICH was associated with functional outcomes but not hematoma expansion.

Numerous studies in the general population and those in patients with coronary heart disease have demonstrated associations between increased HR levels and cardiovascular events and mortality.[13–15] Regarding the absolute HR levels as the prognostic possibilities after stroke, higher HR (≥85 bpm) at baseline was linked to mortality and unfavorable functional outcome both in 5606 patients with acute ischemic stroke in the VISTA study and in 3185 patients with acute ICH in the INTERACT 1 and 2.[4,11] Because various kinds of antihypertensive medications were used in acute ICH in the latter,[11] the

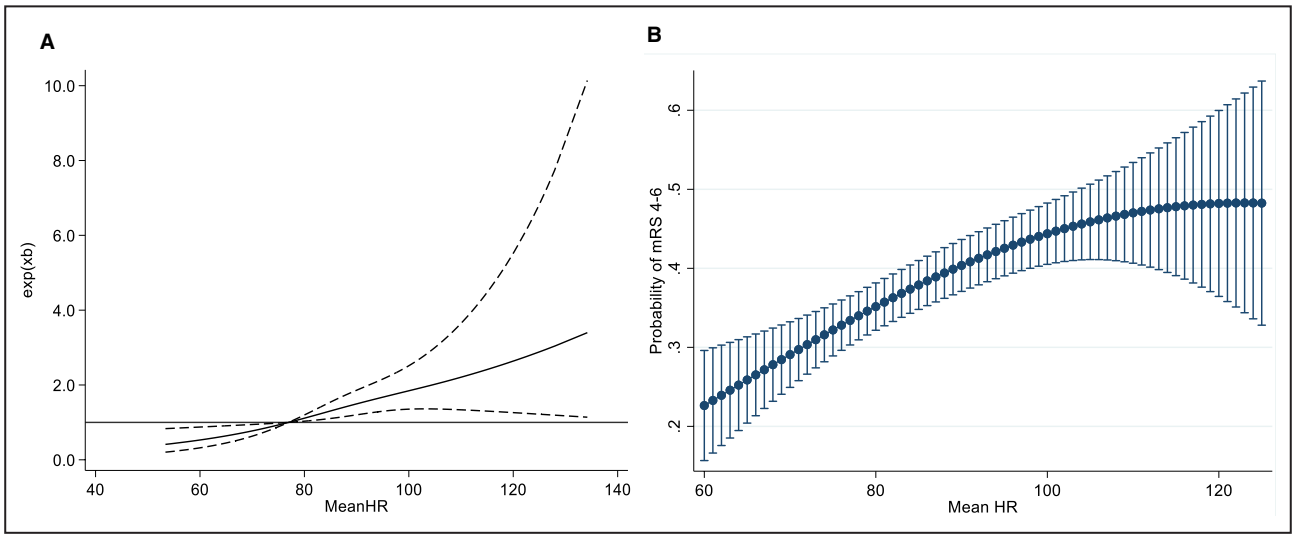


Figure 3. Associations between mean-heart rate (HR) and unfavorable functional outcome.
A, The adjusted cubic spline model. This curve (black line) displays that higher mean HR appears to be associated with a rise in risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1. **B**, Probability of unfavorable functional outcome with margins plot, including 95% CIs. Every 10-bpm increase in the mean HR was associated with an absolute increase in the probability of unfavorable functional outcome by 4.3%.

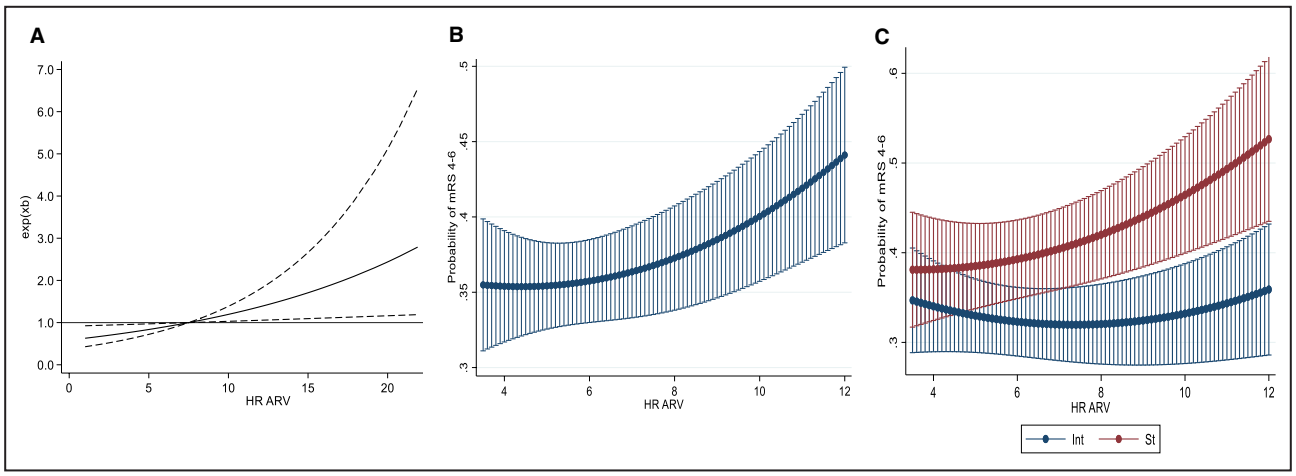


Figure 4. Associations between heart rate- average real variability (HR-ARV) and unfavorable functional outcome.
A, The adjusted cubic spline model. This curve (black line) displays that higher HR-ARV appears to be associated with a rise in the risk of outcome. The dotted curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1. **B**, Probability of unfavorable functional outcome with margins plot, including 95% CIs. Every 1 increase in HR-ARV was associated with an absolute increase in the probability of unfavorable functional outcome by 1.3%. **C**, Probability of unfavorable functional outcome, according to the treatment arm. In the intensive treatment arm, there was a 0.6% increased probability of worse functional outcome per 1 increase in HR-ARV. Whereas in the standard treatment, there was a 2.2% increased probability of it.

association could be independent of nicardipine. The present study is partially in line with the results of the ENOS sub-analysis, showing the positive association between higher HR, HRV (represented by SD of HR), and unfavorable outcome in the setting of all types of acute stroke.[5] Our study confirmed and reinforced the prognostic significance of an increased HR and HRV in a large population with acute ICH of the controlled trial.

Underlying stress conditions related to acute stroke typically cause impaired HR control. Acute stroke per se can commonly provoke autonomic imbalance with activation of the sympathetic nervous system and decreased vagal tone.[16] This sympathetic-vagal dysregulation provokes increased HR and blood pressure, and impaired HRV.[16] Other clinical manifestations have been reported, such as cardiac dysfunction, arrhythmias, hyperglycemia, blood pressure variability, and immunodepression, which lead to worse functional outcome and increased mortality.[3,17] Also, putative mechanisms of sympathetic-vagal dysregulation on the cerebrovascular system have been reported impaired cerebral autoregulation, secondary brain injury due to inflammation, and blood–brain barrier disruption.[18] In particular, lesions involving the insula may disrupt connections to the hypothalamic paraventricular nucleus, although the apparent evidence of relevant localization remains inconclusive.[16]

Furthermore, there is more vigorous use of antihypertensive therapy in the acute period after ICH onset, making the analysis of HR parameters potentially confounded by medication effects. Nicardipine can cause sympathetic activation and reflex sympathetic tachycardia as well-described side effects. However, mean HR and HRV are each associated with clinical outcome independent of intravenous nicardipine. Consequently, HRV represents an inadequate response of the autonomic nervous system insult from acute ICH or other mechanisms and might be used as a potential prognostic indicator in acute ICH.

We showed a linear association between higher mean HR and unfavorable outcomes, which has not been demonstrated previously.[4,19,20] Several observational studies in patients with coronary heart disease suggested a J-shaped association, while whether the J-shaped association between HR and mortality is a prevalent phenomenon across different populations is yet to be established.[21] It is possible that patients with presence of coma with lower HR who may represent the Cushing reflex and typically require surgical evacuation were excluded, thus making them underrepresented in the ATACH-2 trial. Prior studies also have demonstrated associations between HR and mortality in the setting of any stroke.[6] Only 6.6% of participants included in our analyses died at 3 months and may have lacked sufficient power to detect an association.

In contrast, HR-ARV remained associated with both the outcomes. HR-ARV consists of absolute difference between consecutive measurements, which could represent more physiologically relevant HR variation related to concomitant autonomic dysfunction. Also, patients with higher HRV under intensive treatment for elevated BP were more likely to have a moderate risk for worse functional outcome, suggesting that the

potential association might be mediated by intensive BP control. No previous study has focused on the acute term influence of HRV for the outcomes in acute ICH setting, thus limiting comparisons. Collectively, we have interpreted the association between HR-ARV levels, hematoma expansion, and subsequent worse functional outcome manifested as representing a more severe ICH which concomitantly causes more severe autonomic dysfunctions.

The present study focused on intermittent, long-term (1-hour frequency) HRV in the acute stages. Most studies assessing HRV examined beat-to-beat HRV obtained by 24-hour electrocardiographic monitoring.[22,23] The prognostic implications of HRV depend on the measurement method and sampling frequency. It is still uncertain whether a clinical significance of long-term HRV is equivalent to that of beat-to-beat HRV. However, several population-based studies provided evidence that the predictive power of increased long-term HRV obtained every 30 minutes or 1 hour is an independent predictor of cardiovascular events and mortality.[24,25] Therefore, it is possible that intermittent HR monitoring (1-hour frequency) may be effective in predicting prognostic values in clinical settings.

The strength of this study was high frequency sampling of 27 measurements, particularly during the acute phase for the initial 24 hours, which enabled a detailed assessment of intermittent HR fluctuations. This study also has limitations. First, although based on prospectively collected data of a randomized clinical trial, our analysis was post hoc and therefore prone to confounding. Second, selection bias could be considered because of exclusion of patients with huge hematoma from registration, limiting the strength of association and generalizability. Third, reverse causality cannot be excluded in this observational analysis because the more severe ICH subjects with a worse prognosis might give rise to greater HR rather than HR per se causing poor outcome. The independent contribution of HRV even after adjustment for stroke severity argues against, but does not rigorously exclude, reverse causality. Fourth, while we acknowledge the over-inflation of type I error probability from multiple testing, since this work is considered as hypothesis generating.

In conclusion, increased mean HR and HR-ARV within 24 hours after ICH can be an important determinant of outcome. It would be important not only to rapidly reduce high HR but also to ensure that HR control is smooth and sustained in the hyperacute phase of ICH. However, it remains unknown whether modulation of HR could improve prognosis after ICH. Further studies are necessary to confirm our findings and to investigate the clinical implications and optimal HR management strategies in the acute period after ICH.

ARTICLE INFORMATION

Received February 9, 2021; accepted April 28, 2021.

Affiliations

Department of Cerebrovascular Medicine (K.M., M.K., K.T., S.Y., K.T.), Center for Advancing Clinical and Translational Sciences (M.F., H.Y.), and Department of Neurology (M.I.), National Cerebral and Cardiovascular Center, Suita, Japan; and Zeenat Qureshi Stroke Institute and Department of Neurology, University of Missouri, Columbia, MO (A.I.Q.).

Acknowledgments

We thank Prof. Yuko Y. Palesch and Dr K. Omae for providing expertise regarding the statistical analyses.

Sources of Funding

This work was supported by grants from the Japan Agency for Medical Research and Development (AMED 20lk0201094h0002 and 20lk0201109h0001).

Disclosures

Toyoda reports honoraria from Daiichi-Sankyo, Bayer Yakuhin, Brystol-Meyers-Squibb, and Nippon Behringer Ingerheim, outside the submitted work. Koga reports honoraria from Bayer Yakuhin, BMS/Pfizer, Otsuka, Daiichi-Sankyo, Nippon Boehringer Ingelheim and Takeda, scientific advisory board from Ono, and research supports from Takeda, Daiichi-Sankyo, Nippon Boehringer Ingelheim, Astellas, Pfizer and Shionogi, outside the submitted work. Ihara reports grants from Otsuka Pharmaceutical Ltd., grants from BMS, and grants from Shimadzu Corporation outside the submitted work. The remaining authors have no disclosures to report.

Supplementary Material

Table S1
Figure S1

REFERENCES

1. Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. *JAMA*. 2019;321:1295–1303. DOI: 10.1001/jama.2019.2413.
2. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, Anderson CS, et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol*. 2019;18:857–864. DOI: 10.1016/S1474-4422(19)30196-6.
3. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. *Clin Exp Hypertens*. 2004;26:637–644. DOI: 10.1081/CEH-200031959.
4. Nolte CH, Erdur H, Grittner U, Schneider A, Piper SK, Scheitz JF, Wellwood I, Bath PMW, Diener H-C, Lees KR, et al. Impact of heart rate on admission on mortality and morbidity in acute ischaemic stroke patients—results from VISTA. *Eur J Neurol*. 2016;23:1750–1756. DOI: 10.1111/ene.13115.
5. Appleton JP, Woodhouse LJ, Bereczki D, Berge E, Christensen HK, Collins R, Gommans J, Ntaios G, Ozturk S, Szatmari S, et al. Effect of glyceryl trinitrate on hemodynamics in acute stroke. *Stroke*. 2019;50:405–412. DOI: 10.1161/STROKEAHA.118.023190.
6. Erdur H, Scheitz JF, Grittner U, Laufs U, Endres M, Nolte CH. Heart rate on admission independently predicts in-hospital mortality in acute ischemic stroke patients. *Int J Cardiol*. 2014;176:206–210. DOI: 10.1016/j.ijcard.2014.07.001.
7. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-heart interaction: cardiac complications after stroke. *Circ Res*. 2017;121:451–1468. DOI: 10.1161/CIRCRESAHA.117.311170.
8. Wu L, Jiang Z, Li C, Shu M. Prediction of heart rate variability on cardiac sudden death in heart failure patients: a systematic review. *Int J Cardiol*. 2014;174:857–860. DOI: 10.1016/j.ijcard.2014.04.176.
9. Patel VN, Pierce BR, Bodapati RK, Brown DL, Ives DG, Stein PK. Association of Holter-derived heart rate variability parameters with the development of congestive heart failure in the Cardiovascular Health Study. *JACC Heart Fail*. 2017;5:423–431. DOI: 10.1016/j.jchf.2016.12.015.
10. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, et al. Intensive blood-pressure

lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. DOI: 10.1056/NEJMoa1603460.
11. Qiu M, Sato S, Zheng D, Wang X, Carcel C, Hirakawa Y, Sandset EC, Delcourt C, Arima H, Wang J, et al. Admission heart rate predicts poor outcomes in acute intracerebral hemorrhage: the intensive blood pressure reduction in acute cerebral hemorrhage trial studies. *Stroke*. 2016;47:1479–1485. DOI: 10.1161/STROKEAHA.115.012382.
12. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. 2018;17:885–894. DOI: 10.1016/S1474-4422(18)30253-9.
13. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009;150:784–794. DOI: 10.7326/0003-4819-150-11-200906020-00006.
14. Paul L, Hastie CE, Li WS, Harrow C, Muir S, Connell JM, Dominiczak AF, McInnes GT, Padmanabhan S. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension*. 2010;55:567–574. DOI: 10.1161/HYPERTENSIONAHA.109.144808.
15. Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M, Ducimetiere P. Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. *Am J Cardiol*. 2009;103:279–283. DOI: 10.1016/j.amjcard.2008.08.071.
16. De Raedt S, De Vos A, De Keyser J. Autonomic dysfunction in acute ischemic stroke: an underexplored therapeutic area? *J Neurol Sci*. 2015;348:24–34. DOI: 10.1016/j.jns.2014.12.007.
17. Kaye DM, Lambert GW, Lefkovits J, Morris M, Jennings G, Esler MD. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *J Am Coll Cardiol*. 1994;23:570–578. DOI: 10.1016/0735-1097(94)90738-2.
18. Yperzeele L, van Hooff RJ, Nagels G, De Smedt A, De Keyser J, Brouns R. Heart rate variability and baroreceptor sensitivity in acute stroke: a systematic review. *Int J Stroke*. 2015;10:796–800. DOI: 10.1111/ijs.12573.
19. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50:823–830. DOI: 10.1016/j.jacc.2007.04.079.
20. Steinberg BA, Kim S, Thomas L, Fonarow GC, Gersh BJ, Holmqvist F, Hylek E, Kowey PR, Mahaffey KW, Naccarelli G, et al. Increased heart rate is associated with higher mortality in patients with atrial fibrillation (AF): results from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF). *J Am Heart Assoc*. 2015;4:e002031. DOI: 10.1161/JAHA.115.002031.
21. Cook S, Togni M, Schaub MC, Wenaweser P, Hess OM. High heart rate: a cardiovascular risk factor? *Eur Heart J*. 2006;27:2387–2393. DOI: 10.1093/eurheartj/ehl259.
22. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256–262. DOI: 10.1016/0002-9149(87)90795-8.
23. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput*. 2006;44:1031–1051. DOI: 10.1007/s11517-006-0119-0.
24. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, Inoue R, Hoshi H, Hashimoto J, Totsune K, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension*. 2008;52:1045–1050. DOI: 10.1161/HYPERTENSIONAHA.107.104620.
25. Johansson JK, Niiranen TJ, Puukka PJ, Jula AM. Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. *Hypertension*. 2012;59:212–218. DOI: 10.1161/HYPERTENSIONAHA.111.178657.

SUPPLEMENTAL MATERIAL

Table S1. Baseline HR measures between the treatment allocation.

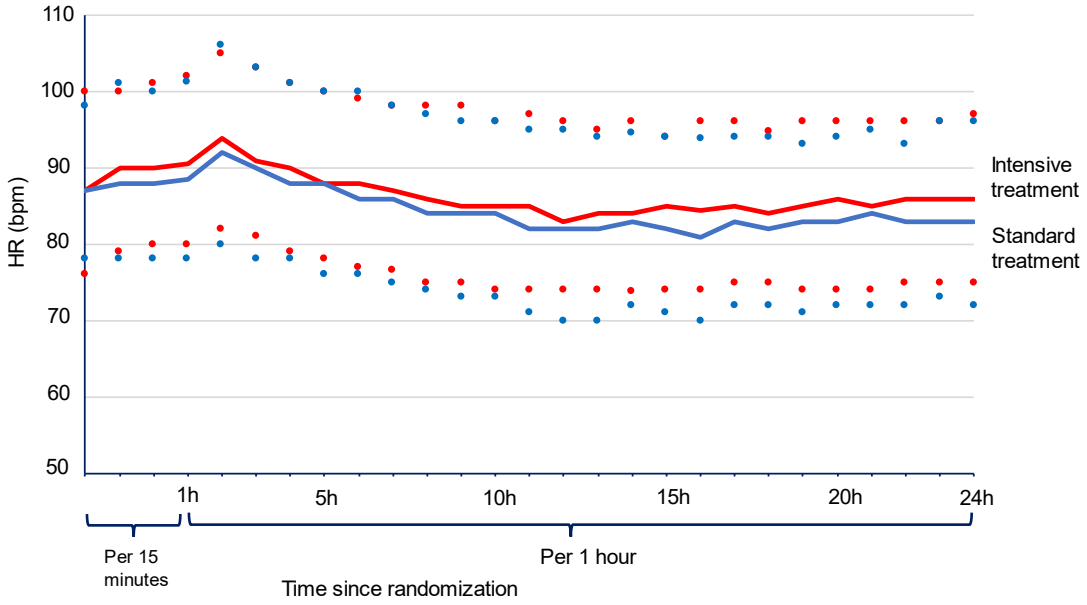
	the intensive-treatment group	the standard-treatment group	p
Mean HR, bpm	87 [77–96]	85 [76–96]	0.053
HR-SD, bpm	8.8 [6.7–11.2]	8.9 [6.8–11.7]	0.302
HR-CV, %	10.0 [7.8–13.1]	10.5 [8.2–13.6]	0.032*
HR-SV, bpm	8.3 [6.2–11.2]	8.5 [6.3–11.5]	0.365
HR-ARV, bpm	6.2 [4.6–8.1]	6.1 [4.7–8.2]	0.445

Values are presented as median [interquartile ranges].

HR, heart rate; ARV, average real variability; CV, coefficient of variation; and SV, successive variation.

*$p < 0.05$.

Figure S1. Within group median mean-HR during the first 24 h after randomization and interquartile range.



The red line (median) and dots (IQR) represent intensive treatment group. The blue line (median) and dots (IQR) represent the standard treatment group.