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Admission Heart Rate Variability is Associated with Fever Development in Patients with Intracerebral Hemorrhage

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Abstract

Background: Fever is associated with worse outcome after intracerebral hemorrhage (ICH). Autonomic dysfunction, commonly seen after brain injury, results in reduced heart rate variability (HRV). We sought to investigate whether HRV was associated with the development of fever in patients with ICH.

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Methods: We prospectively enrolled consecutive patients with spontaneous ICH in a single center observational study. We included patients who presented directly to our emergency department after symptom onset, had a 10-second electrocardiogram (EKG) performed within 24 hours of admission, and were in sinus rhythm. Patient temperature was recorded every 1–4 hours. We defined being febrile as having a temperature of ≥38°C within the first 14 days, and fever burden as the number of febrile days. HRV was defined by the standard deviation of the R-R interval (SDNN) measured on the admission EKG. Univariate associations were determined by Fisher's exact, Mann Whitney U, or Spearman's rho correlation tests. Variables associated with fever at $p \leq 0.2$ were entered in a logistic regression model of being febrile within 14 days.

Results: There were 248 patients (median age 63 [54–74] years, 125 [50.4%] female, median ICH Score 1 [0–2]) who met inclusion criteria. Febrile patients had lower HRV (median SDNN: 1.72 [1.08–3.60] versus 2.55 [1.58–5.72] msec, p= 0.001). Lower HRV was associated with more febrile days ($R = -0.22$, $p < 0.001$). After adjustment, lower HRV was independently associated with greater odds of fever occurrence (OR 0.92 [95% CI 0.87–0.97] with each msec increase in SDNN, p= 0.002).

Conclusions: HRV measured on 10-second EKGs is a potential early marker of parasympathetic nervous system dysfunction and is associated with subsequent fever occurrence after ICH. Detecting early parasympathetic dysfunction may afford opportunities to improve ICH outcome by targeting therapies at fever prevention.

Keywords

Intracerebral Hemorrhage; Fever; Autonomic Dysfunction; Heart Rate Variability

Background

Primary intracerebral hemorrhage (ICH) has the poorest prognosis of all the stroke subtypes, carrying a mortality rate of 59% at one year.[1] Predictors of unfavorable outcome in patients with ICH, include: age, hematoma size and location, intraventricular extension, Glasgow Coma Scale (GCS), and fever.[2,3] Fever in patients after stroke is associated with longer hospital stays, increased mortality, and worse functional outcomes.[3–5]

Autonomic dysfunction is common after stroke. Heart rate variability (HRV) reflects the balance between the sympathetic and parasympathetic tone and their effect on the sinus node, and is thereby considered a marker of autonomic nervous system function.[6,7] Decreased HRV has been demonstrated after both ischemic stroke and ICH, and is associated with unfavorable outcome.[8] Several mechanisms have been proposed to explain the association between autonomic nervous system dysfunction and worse outcome, including: impaired cerebral autoregulation, cardiovascular complications, blood pressure fluctuations, and secondary brain injury due to inflammation, hyperglycemia, and blood-brain barrier disruption.[9] We hypothesized that parasympathetic nervous system dysfunction after ICH may contribute to subsequent fever, which in turn contributes to worse functional outcome. Therefore, we sought to test the hypothesis that initial HRV is an early marker of parasympathetic dysfunction and is associated with fever in patients after intracerebral hemorrhage.

Methods

Study Population:

Patients presenting directly to the Northwestern Memorial Hospital emergency department with spontaneous ICH between December 2006 and March 2016 were prospectively enrolled in an observational study. Patients with ICH secondary to trauma, hemorrhagic conversion of ischemic stroke, or structural lesions (i.e. aneurysm, tumor, arteriovenous malformation, and vasculitis) were excluded. All cases of ICH were diagnosed by a board-certified vascular neurologist or neurointensivist utilizing computerized tomography. Within 24 hours of admission to the hospital, a 10-second twelve-lead electrocardiogram (EKG) was obtained for each patient in resting, supine position using a GE Marquette MAC 5500 EKG machine. In the case of multiple EKGs, the first EKG was used for analysis. A board-certified cardiologist read and interpreted each EKG. In order to be included in this study the EKG needed to demonstrate sinus rhythm; EKGs showing atrial fibrillation or other arrhythmias were excluded.

The Institutional Review Board (IRB) approved this study. Consent was obtained from the patient or a legally authorized representative. The IRB approved a waiver of consent for patients who died during hospitalization, or were incapacitated and for whom a legal representative could not be located.

Clinical Variables:

Demographic information, medical history, standardized clinical instruments (Glasgow Coma Scale [GCS], National Institute of Health Stroke Scale [NIHSS], and ICH Score [a common disease severity score with increasing severity from 0 to 6]), admission blood pressure, medical complications, imaging data (including initial hematoma volume measured by pixel thresholding technique and semi-quantitative intraventricular hemorrhage volume [Graeb score])[10,11], therapeutic interventions, and laboratory data were prospectively recorded. Beta blocker exposure was defined as premorbid use or administration of any beta blocker medication within the first 24 hours of hospitalization.

A certified examiner prospectively assessed modified Rankin Scores (mRS, a functional outcome scale from 0 [no symptoms] to 6 [dead]) at 3 months after ICH onset. The mRS was determined by structured telephone interview using a validated questionnaire.[12,13]

HRV was defined as the standard deviation of the R-R intervals (SDNN) between normally conducted QRS complexes on the admission 10-second EKG. We also calculated the root mean square of successive R-R interval differences (RMSSD) as a secondary measure of HRV. While both sympathetic and parasympathetic nervous system activity contribute to SDNN, parasympathetic activity is the predominant source of variation during short recordings because of the low frequency range of sympathetic nervous system activity; in addition, RMSSD primarily represents parasympathetic vagally mediated changes in HRV.[14] Although a 10-second EKG likely yields a less precise estimate of SDNN and RMSSD than longer recordings, 10-second EKGs are routinely acquired in clinical practice and are permanently recorded for analysis. Furthermore, SDNN and RMSSD from 10-second EKGs are strongly correlated with these measures on 4–5 minute recordings (Pearson's rho >0.75)

and the 10-second EKG technique has been previously validated.[15,16] HRV was determined from the digital Extensible Markup Language (XML) version of each EKG, which ensured reproducibility of R-R interval measurements.

We prospectively recorded the presence of temperature ≥38°C from the day of ICH through 14 days after ICH onset. Temperatures were recorded every 1–2 hours in the intensive care unit and every 2–4 hours outside of the intensive care unit, and entered into the electronic medical record. We obtained core (rectal or esophageal) temperatures in all mechanically ventilated patients or patients with an oral temperature ≥38°C. Fever was treated with acetaminophen and surface cooling methods (ice packs and Medi-therm III cooling blankets [Gaymar, Inc., Orchard Park, NY]) on a routine basis. We did not routinely use Arctic Sun (blanket), Innercool (indwelling catheter) or similar devices. Patients were categorized as having been febrile if they had a temperature ≥38°C at any time within 14 days of ICH onset. Fever burden was defined as the number of days with temperature ≥38°C, a definition which correlates well with alternative definitions of fever burden.[17]

Statistical Analysis:

Descriptive summaries are provided as frequency (percentage), mean ± SD for normally distributed variables, and median and interquartile range (Q1-Q3) for non-normally distributed variables. Categorical data were compared using Fisher's exact test or chi-square test as appropriate. For non-parametric data, Mann-Whitney U test was used to compare characteristics between groups. Spearman correlation test was used to examine associations with number of days febrile. Variables that were univariately associated with occurrence of fever at $p \leq 0.2$ were entered into a binary logistic regression model of fever occurrence. A backward stepwise selection technique with removal criterion of probability of F to remove ≥ 0.1 was used to generate a parsimonious model. To confirm that the associations between HRV metrics and fever were independent of heart rate, we repeated the binary logistic regression models using SDNN and RMSSD standardized to heart rate; standardized SDNN and RMSSD were obtained by dividing the respective metric by the average R-R interval. We also performed a secondary analysis to identify predictors of number of days febrile (i.e. count data) using a generalized linear model with a negative binomial distribution, again utilizing the backward stepwise selection technique to generate a parsimonious model. We also confirmed previously reported associations between fever and unfavorable functional outcome (mRS 4–6) at three months by including fever and ICH Score in a binary logistic regression model of functional outcome at three months.

Statistical analysis was performed using SPSS v.25 (IBM, Armonk NY) and p values < 0.05 were considered significant.

Results

We identified 248 patients (median age 63 [54–74] years, 125 [50.4%]) female, median ICH Score 1 [0–2]) with primary ICH who met inclusion criteria, of whom 132 (53%) were febrile within the 14 days following ICH onset. The median number of days febrile was 1 (0–5). The patient's baseline demographics and clinical variables by febrile status are shown in Table 1. Patients who developed fever had higher heart rates (median 85 [74–99] vs. 80

[70–91] beats/minute, p = 0.02), lower HRV (SDNN, median 1.72 [1.08–3.60] vs. 2.55 [1.58–5.72] msec, p = 0.001), and less beta blocker exposure (68 [51.5%] vs. 75 [64.7%], p=0.04). Additionally, lower HRV was associated with greater fever burden (SDNN vs. febrile days, rho −0.22, p < 0.001). Patients who developed fever had lower admission GCS (median 11 [7–14] vs. median 15 [13–15], p < 0.001), larger hematoma volumes (median 16.5ml [5.4–36] vs. 5.5ml [2.4–14], p < 0.001), and greater intraventricular hemorrhage (initial Graeb score, median 2 [2–6] vs. 0 [0–1], p < 0.001). In addition, patients who developed fever spent more time mechanically ventilated (i.e. fewer ventilator free days in the first two weeks, median 6.5 [1–14] vs. 14 [14–14] days, p < 0.001) and were more likely to be diagnosed with pneumonia during hospitalization (25% vs. 1.7%, p < 0.001). While mechanical ventilation was associated with fever, SDNN and standardized SDNN did not significantly differ by mechanical ventilation status (p=0.13 and p=0.37, respectively). Furthermore, Spearman correlations for SDNN and RMSSD with admission GCS (p=0.12 and p=0.80, respectively) and ICH Score (p=0.55 and p=0.10, respectively) were not statistically significant.

In the primary analysis (Table 2), we found that decreased HRV measured by SDNN was independently associated with greater odds of fever occurrence within the 14 days following ICH onset (OR 0.92 [95% CI 0.87–0.97] per msec increase in SDNN, p = 0.002). Initial Graeb score, ventilator free days, diagnosis of pneumonia, and history of hypertension were also independently associated with the occurrence of fever. In the analysis of fever burden (Table 2), decreased HRV measured by SDNN was an independent predictor of days febrile (incidence rate ratio 0.97 [95% CI 0.94–0.99] times the rate of fever per msec increase in SDNN, p = 0.015). Other variables associated with fever burden included diagnosis of pneumonia, ventilator free days, initial hematoma volume, and initial Graeb score. HRV measured by RMSSD was also independently associated with fever occurrence and fever burden (Table 2). Associations between fever occurrence and HRV remained significant when standardized SDNN and standardized RMSSD were substituted in parsimonious models (p=0.018 and p=0.003, respectively; Supplemental Table).

Three-month functional outcomes were available for 179 (72.2%) patients. In multivariate analysis for unfavorable functional outcome (mRS 4–6 at three months) we found that fever, whether modeled as a binary variable for fever occurrence (OR 5.80 [95% CI 2.60–12.9], p < 0.001) or as the count of days febrile (OR 1.18 [95% CI 1.04–1.33] per day, p = 0.011), was independently associated with unfavorable functional outcome after accounting for the ICH Score (Table 3). While SDNN was associated with fever, and fever was associated with functional outcome, the SDNN itself was not associated with unfavorable functional outcome after accounting for the ICH Score.

Discussion

We found that decreased HRV on 10-second EKGs is associated with greater occurrence and burden of fever after spontaneous ICH. We also demonstrated, as previously shown by others, that fever after ICH is associated with worse functional outcome.[3,5] However, in our cohort, HRV as measured on 10-second EKG was not itself significantly associated with functional outcome after accounting for ICH severity. These findings are consistent with our

hypothesis that early HRV reflects the risk of subsequent fever, but that fever, rather than HRV, is the more proximate factor that influences outcome after ICH. Decreased RMSSD and SDNN measured on short duration recordings is consistent with parasympathetic nervous system dysfunction in particular;[14] relative sympathetic hyperactivity resulting from impaired parasympathetic function is a plausible mechanism by which parasympathetic dysfunction could contribute to fever.[18] Alternatively, multiple lines of research suggest that activation of vagal nerve cholinergic efferent nerves has an anti-inflammatory effect and that parasympathetic dysfunction can contribute to inflammation; inflammation associated with parasympathetic dysfunction could subsequently contribute to fever development.[19–21] These data are also consistent with a growing body of evidence supporting fever after stroke as a mechanism of brain injury and worse neurologic outcome.[4] ICH is a highly morbid disease with limited specific interventions but multiple contributors to unfavorable outcome. Therefore, a potentially modifiable contributor to secondary brain injury, such as fever, is an attractive target for intervention. Our study is impactful in that it suggests that it is possible to identify patients at highest risk for fever early in their disease course, and that parasympathetic dysfunction beginning early after ICH onset may contribute to subsequent fever.

There are various methods to analyze HRV including linear time-domain variables (SDNN and RMSSD), frequency-domain parameters (low-frequency power and high-frequency power), and more recently non-linear parameters utilizing multiscale entropy.[7,14,22–24] In this study we utilized HRV calculated as the standard deviation of normal R to normal R intervals (SDNN) on 10-second standard hospital admission EKG's as our primary metric of HRV. This method has previously been validated as an accurate measure of HRV, is strongly correlated with SDNN from 4–5 minute recordings, and is representative of parasympathetic function when compared to prolonged heart rate monitoring methods.[15,16,25] HRV on 10-second EKGs has also been used to investigate relationships between parasympathetic dysfunction and cognitive and functional decline in the elderly and risk of cardiac mortality.[15,26,27] HRV has been studied using longer time durations such as 5-minute and 24-hour recordings, and these approaches may provide the benefit of greater opportunity to assess variability, response to activity, and the influence of circadian rhythms. In addition, while the primary source of variation during short duration recordings is parasympathetic activity, longer duration recordings are expected to reflect the contribution of sympathetic activity, which acts over a lower frequency range.[14] However, longer duration recording represents greater demands on data management and storage infrastructure and may not be as practical as short duration recording in the intensive care environment. In our study, short duration recording allowed us to assess patients' parasympathetic nervous system status earlier in their disease course than would have been possible with longer duration recordings. It is noteworthy that HRV assessed on short duration recordings would be expected to bias towards null findings; despite this expectation, we were able to demonstrate significant associations between parasympathetic dysfunction characterized by 10-second HRV and fever occurrence.

There are limitations to these data. This study was performed at a single center that is a tertiary referral center; our patient demographics may not be the same as other institutions. While we routinely use temperature management strategies with acetaminophen and surface

cooling methods (ice packs and Medi-therm III cooling blankets) it is difficult to know how the routine implementation of cooling methods such as Arctic Sun (blanket) or Innercool (indwelling catheter) would have affected our findings with fever burden. We recorded the number of days febrile rather than an area under the temperature curve as our measure of fever burden; however, prior studies suggest these approaches yield similar results.[17] Another limitation of our study is a possible discrepancy in fever detection using oral rather than rectal temperatures in selected patients; however, studies on the inter-method reliability of temperature using electronic sensors has shown that the difference in reliability between oral and rectal measures is small and not systematically biased.[28,29]

Recent studies have implicated decreased HRV as a marker of outcome in both hemorrhagic and ischemic stroke.[7,8,30] However, we did not identify a direct statistical association between HRV and functional outcome after accounting for the ICH score. This difference may result from our analyses representing HRV with linear methods (SDNN and RMSSD) from 10-second EKG in the acute setting, while other studies used combinations of non-linear methods or frequency-domain analysis, longer duration recordings (typically 1 to 24 hours), and/or recording after the acute time period. While there are multiple valid approaches to assess HRV, some researchers have suggested that multi-scale entropy is a better powered technique to predict long-term outcomes after stroke.[31,32] Additionally, it is possible that sympathetic nervous system dysfunction influences outcome and 10-second recordings, which primarily reflect parasympathetic nervous system function, do not adequately represent sympathetic nervous system contributions. It should be noted that our findings do not preclude the possibility of additional mechanisms by which autonomic dysfunction may impact outcome after ICH, including: impaired cerebral autoregulation, cardiovascular complications, blood pressure fluctuations, and secondary brain injury due to inflammation, hyperglycemia, and blood-brain barrier disruption.[9] Furthermore, it should be acknowledged that parasympathetic dysfunction may be coincident with fever and other factors predictive of outcome, but parasympathetic dysfunction itself may not be pathologic.

Conclusion

Our study provides evidence that heart rate variability measured on 10-second EKGs is a marker of parasympathetic dysfunction associated with subsequent fever occurrence and fever burden in patients with ICH. Our study also suggests that this parasympathetic dysfunction can be detected early after ICH onset. Improving the detection of parasympathetic dysfunction early after ICH may afford opportunities to improve ICH outcome by targeting therapies at fever prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Patient Demographics and Clinical Variables by Presence of Fever

	Patients without fever (n=116)	Patients with fever (n=132)	P-value
Age	64 ± 15	64 ± 13	0.07
Sex (Female)	62 (53.4%)	63 (47.7%)	0.38
Race			
Black or African American	43 (37.1%)	59 (44.7%)	0.46
White/Caucasian	65 (56.0%)	66 (50.0%)	
Other	8 (6.9%)	7 (5.3%)	
Admission GCS	15 (13–15)	11 (7–14)	< 0.001
Admission NIHSS	5.5 (2–10)	16 (5–22)	< 0.001
Initial Hematoma Volume, ml	5.5 (2.4–14)	16.5 (5.4–36)	< 0.001
Intraventricular Hemorrhage Present	31 (26.7%)	73 (55.3%)	< 0.001
Initial Graeb Score	0 (0–1)	2 (2–6)	< 0.001
Lobar Location	38 (32.8%)	55 (41.7%)	0.19
ICH Score	1 (0–1)	2 (1–3)	< 0.001
Initial Systolic Blood Pressure, mmHg	190 (158–216)	190 (152–223)	0.60
International Normalized Ratio (INR)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.91
Warfarin Use	7 (6.0%)	11 (8.3%)	0.63
Beta Blocker Exposure	75 (64.7%)	68 (51.5%)	0.04
History of Hypertension	94 (81.0%)	90 (68.2%)	0.03
History of Diabetes Mellitus	27 (23.3%)	30 (22.7%)	0.99
History of Ischemic Stroke	15 (12.9%)	19 (14.4%)	0.85
History of Coronary Artery Disease	15 (12.9%)	20 (15.2%)	0.72
Ventilator Free Days	14 (14–14)	6.5 (1–14)	< 0.001
Pneumonia During Hospitalization	2 (1.7%)	33 (25%)	< 0.001
Heart Rate, per minute	80 (70–91)	85 (74–99)	0.02
R-R Interval, msec	189 (164–216)	176 (151–202)	0.01
HRV by SDNN, msec	2.55 (1.58–5.72)	1.72 (1.08–3.60)	0.001
HRV by Standardized SDNN	0.013 (0.008–0.026)	0.010 (0.007–0.018)	0.003
HRV by RMSSD, msec	2.36 (1.28–5.08)	1.74 (1.19–4.08)	0.08
HRV by Standardized RMSSD	0.031 (0.016–0.069)	0.021 (0.014–0.056)	0.03

GCS = Glasgow Coma Scale, HRV = heart rate variability, ICH = intracerebral hemorrhage, NIHSS = National Institutes of Health Stroke Scale, RMSSD = root mean square of successive R-R interval differences, SDNN = standard deviation of the R-R interval.

Table 2.

Parsimonious Models Predicting Fever

SDNN (Primary HRV Metric)			
Variable	**OR**	**CI 95%**	**P-value**
Occurrence of Fever			
HRV by SDNN, msec	0.92	0.87–0.97	0.002
Admission GCS	0.88	0.78–1.01	0.060
Initial Graeb Score	1.15	1.01–1.31	0.032
Ventilator Free Days	0.91	0.84–0.98	0.010
Pneumonia	9.16	1.94–43.4	0.005
Lobar Hematoma	1.81	0.95–3.45	0.070
History of Hypertension	0.47	0.23–0.95	0.034
Variable	IRR	CI 95%	P-value
Number of Days Febrile			
HRV by SDNN, msec	0.97	0.94–0.99	0.015
Initial Graeb Score	1.11	1.06–1.16	< 0.001
Ventilator Free Days	0.91	0.88–0.94	< 0.001
Pneumonia	2.28	1.49–3.49	< 0.001
History of Hypertension	0.71	0.50–1.03	0.069
Initial Hematoma Volume	1.01	1.00–1.02	0.007
RMSSD (Secondary HRV Metric)			
Variable	OR	CI 95%	P-value
Occurrence of Fever			
HRV by RMSSD, msec	0.958	0.921–0.996	0.030
Initial Graeb Score	1.17	1.04–1.32	0.010
Ventilator Free Days	0.90	0.84–0.97	0.003
Pneumonia	10.5	2.29–47.6	0.002
History of Hypertension	0.44	0.22–0.88	0.020
Initial Hematoma Volume	1.02	1.00–1.04	0.037
Variable	IRR	CI 95%	P-value
Number of Days Febrile			
HRV by RMSSD, msec	0.978	0.957–0.999	0.040
Initial Graeb Score	1.11	1.06–1.17	< 0.001
Ventilator Free Days	0.91	0.88–0.94	< 0.001
Pneumonia	2.22	1.45–3.39	< 0.001
History of Hypertension	0.73	0.51–1.05	0.087
Initial Hematoma Volume	1.01	1.00–1.02	0.003

Variables assessed for parsimonious model inclusion included: age, heart rate variability (SDNN and RMSSD), admission Glasgow Coma Scale score, initial Graeb score, initial hematoma volume, days free of mechanical ventilation, diagnosis of pneumonia during hospitalization, lobar hematoma location, history of hypertension, and beta blocker exposure.

CI = confidence interval, GCS = Glasgow Coma Scale, HRV = heart rate variability, IRR = incidence rate ratio, OR = odds ratio, RMSSD = root mean square of successive R-R interval differences, SDNN = standard deviation of the R-R interval.

Table 3.

Regression Models Predicting Outcome

Variable	OR	CI 95%	P-value
Unfavorable Outcome mRS 4–6			
Fever Occurrence	5.80	2.60–12.9	< 0.001
ICH Score	3.28	2.19–4.91	< 0.001
Unfavorable Outcome mRS 4–6			
Days Febrile	1.18	1.04–1.33	0.011
ICH Score	3.06	2.05–4.57	< 0.001

CI= confidence interval, ICH = intracerebral hemorrhage, mRS = Modified Rankin Score, OR = odds ratio.