Original Communication

Correlation between clinical severity and extent of autonomic cardiovascular impairment in the acute phase of subarachnoid hemorrhage

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Abstract
Background and aim To assess associations between clinical severity and possible dysfunction of autonomic cardiovascular modulation within the acute phase after spontaneous subarachnoid hemorrhage (SAH).

Methods In this prospective observational study, in 51 patients with spontaneous SAH, Hunt-and-Hess scores (H&H) were assessed and cardiovascular autonomic modulation was monitored within 24 h after SAH-onset. From 5 min time-series of R–R-intervals (RRI) and blood-pressure (BP) recordings, we calculated autonomic parameters including time-domain [RRI-coefficient-of-variation (RRI-CV) and square-root-of-the-mean-squared-differences-of-successive-RRIs (RMSSD)] and frequency-domain parameters [low- and high-frequency-powers of RRI- and BP-modulation (RRI-LF-, RRI-HF-, SBP-LF-powers) and RRI-total-powers]. Data were compared to those of 20 healthy volunteers.

Results RRI- and BP-values did not differ between groups. Yet, parameters of sympathetic (RRI-LF-powers 141.0 (18.9–402.4) ms² vs 442.3 (246.8–921.2) ms², \(p = 0.001\)) and total autonomic modulation (RRI-CV 2.4 (1.2–3.7) ms² vs 3.7 (3.1–5.3) ms², \(p = 0.001\)) were significantly lower in patients than in controls. Subgroup analyses (patients with H&H <3 vs H&H ≥ 3) and Spearman-rank-correlations revealed increasing loss of sympathetic (RRI-LF-powers 338.6 (179.7–710.4) ms² vs 72.1 (10.1–175.9) ms², \(p = 0.001\), rho = −0.524) and total autonomic modulation (RRI-CV 3.5 (2.3–5.4) ms² vs 1.6 (1.0–2.8) ms², \(p < 0.001\), rho = −0.519) with higher H&H-scores. Multiple-logistic-regression underlined the significant influence of H&H-scores on sympathetic (RRI-LF-powers, \(p = 0.033\)) and total autonomic modulation (RRI-CV, \(p = 0.040\)) compared to possible confounders (e.g., age, intubation).

Conclusion Within the acute phase, spontaneous SAH induces a decrease in sympathetic and total autonomic cardiovascular modulation. Higher H&H-scores were associated with increasing autonomic dysfunction and may therefore augment the risk of cardiovascular complications and poor clinical outcome.

Keywords Subarachnoid hemorrhage · Autonomic nervous system · Hunt and Hess · Heart rate variability

Introduction

Non-traumatic subarachnoid hemorrhage (SAH) represents a significant cause of morbidity and mortality throughout the world [1–3]. Although neurological complications, e.g., re-bleeding, hydrocephalus, seizures, and delayed cerebral ischemia, represent relevant aspects that may lead to death and disability after spontaneous SAH, systemic complications may also negatively affect functional outcome [1, 2]. Systemic complications include electrocardio-graphic changes, troponin elevation, neurogenic stunned myocardium, pulmonary edema, anaemia, or hyponatraemia—i.e., conditions that have been associated with a systemic
catecholamine release and sympathetic nervous system activation [1, 2].

In several neurological diseases with focal parenchymal injury, e.g., traumatic brain injury (TBI), ischemic stroke, or intracranial haemorrhage, previous studies demonstrated autonomic cardiovascular dysfunction with a decline of overall autonomic modulation and a shift towards sympathetic dominance [4]. So far, only a few studies assessed cardiovascular autonomic modulation after SAH. However, these studies reported contradictory results and only assessed changes of sympathetic and vagal cardiac modulation and heart rate variability (HRV) within the first few days after SAH. Hence, there is uncertainty on initial trauma-induced changes of autonomic cardiovascular modulation compared to healthy persons. Furthermore, there are no studies assessing possible associations between clinical impairment and cardiovascular modulation within the acute phase of the disease as a potentially important marker affecting morbidity and mortality.

We hypothesize that the degree of acute clinical deficits is associated with an increasing risk of autonomic cardiovascular dysfunction. Therefore, we prospectively assessed cardiovascular autonomic modulation within 24 h after spontaneous SAH compared to healthy volunteers, and determined correlations between parameters of autonomic modulation and Hunt-and-Hess scores (H&H) in spontaneous SAH patients.

Methods

Patient selection

All patients with SAH admitted to the neuro-emergency department of the Friedrich-Alexander-University Hospital Erlangen-Nuremberg (FAU), Germany, between 09/2018 and 09/2019 were screened for eligibility to participate in the present study. Inclusion criteria consisted of (i) absence of trauma or cerebral amyloid angiopathy as primary cause of SAH, (ii) perimesencephalic SAH, (iii) in-hospital treatment on IMC or neuro-ICU, and (iv) autonomic testing within 24 h after symptom onset (Fig. 1). The study was approved by the ethics committee of the University of Erlangen-Nuremberg, and written informed consent has been obtained from all study participants or their legal representatives according to the Declaration of Helsinki.

Clinical and radiological parameters

Upon hospital admission, H&H for acute clinical grading (ranging from 1 to 5 with a higher score indicating more severe clinical condition) and the pre-stroke modified Rankin Scale (pre-mRS; ranging from 0 to 5, grading patient’s disability prior to the incident) were assessed. We retrieved data on demographic parameters, prior comorbidities, as well as relevant premedication from the institutional electronic databases. Moreover, we collected data from the initial emergency therapy, i.e., usage of analgesic and sedative drugs, catecholamines, intubation and mechanical ventilation, or CSF drainage via EVD, that patients received before or during autonomic measurement (Table 1 and Suppl-Table 1).

Diagnosis of SAH was made upon cranial computed tomography (CT) imaging (Somatom Definition AS +) or spinal tap (xanthochromia and more than 2000 red blood cells/µl) [5]. CT-scans were reviewed by three neuroradiologists blinded to clinical parameters. Investigators documented concomitant intracerebral hemorrhage, intraventricular hemorrhage (IVH), and acute hydrocephalus (enlargement of lateral ventricles measured as bicaudate index > 95th percentile for age; Table 1) [6]. The decision to perform digital subtraction angiography for detection of the source of bleeding followed by endovascular or surgical treatment of aneurysm if applicable was made by the treating physician.

Upon hospital discharge, clinical outcome, i.e., mRS, as a functional parameter for disability was assessed (ranging from 0 to 6, with values of 0–3 indicating favourable outcome and 4–6 indicating unfavourable outcome; Table 1).

Parameters of autonomic cardiovascular modulation

Within 24 h after symptom onset, parameters of cardiovascular autonomic modulation were monitored via 3-lead electrocardiography (sampled at 200 Hz) for 5 min time-series of R–R-intervals (RRI) and beat-to-beat systolic and diastolic blood pressure (SBP, DBP) with non-invasive measurement via finger pulse photoplethysmography (Portapres®, TPD Biomedical Instrumentation, Amsterdam, The Netherlands) at the index or middle finger [7]. The blood pressure (BP) was calibrated against the ipsilateral brachial artery BP [7]. Analysis of the digitized data was performed on a customized data acquisition and analysis system (SUEmpathy™, SUESS Medizin-Technik GmbH, Aue, Germany) [8].

Within the 5 min recordings, the most stationary 2 min segments (i.e. clear signals without arrhythmias) were extracted followed by manual correction of artefacts and calculation of the mean values and standard deviation (SD) of all signs.

From the 2 min segments, time-domain parameters of cardiovascular autonomic modulation were calculated, i.e., the coefficient of variation of RRI (RRI-CV) and the RRI-SD both reflecting sympathetic and vagal cardiac modulation as well as square root of the mean squared differences.
of successive RRIs (RMSSD) which is assumed to uniquely reflect vagal cardiac modulation [4, 9, 10].

RRI- and BP-values show slow underlying fluctuations that are largely mediated by undulating activity of the autonomic nervous system (ANS) [11]. We performed spectral analysis of slow sympathetically and parasympathetically mediated RRI and BP oscillations, using trigonometric regressive spectral analysis (TRS) algorithm [7]. The TRS algorithm identifies two main peaks of oscillation of RRI and BP modulation: the low-frequency (LF; 0.04–0.14 Hz) and high-frequency (HF; 0.15–0.50 Hz) range [4, 9, 10]. The magnitude of LF and HF oscillations can be calculated as integral under the power spectral density curves of RRI (ms²/Hz) and BP (mmHg²/Hz), and is then defined as LF- and HF-powers of RRI (ms²) and BP (mmHg²) [4, 9, 10].

LF oscillations of RRI at rest (RRI-LF-powers) are described to be influenced by sympathetic outflow and also, to an uncertain degree, by parasympathetic outflow [4, 9, 10]. On contrary, LF oscillations of BP (SBP-LF-powers) are solely depending upon sympathetic outflow [4, 9, 10]. HF oscillations of RRI (RRI-HF-powers) are related to parasympathetic outflow, whereas fluctuations in the HF range of BP are mainly caused by respiration-induced fluctuations in venous return and cardiac output [4, 9, 10].

As an additional parameter for total autonomic cardiac modulation, we determined total powers of RRI oscillations (RRI-total powers) as sum of LF- and HF-powers. Finally, RRI-LF/HF-ratios were calculated as an index for sympatho-vagal balance [4, 9, 10].

Cardiovascular autonomic parameters of patients were compared to data of 20 healthy volunteers with no prior cardiovascular diseases or medication. Healthy controls were tested between 9AM and 2PM in supine position in a quiet room with ambient temperature of approximately 24 °C and stable humidity. Before testing, participants initially rested for 40 min to ensure a stable cardiovascular situation.

Fig. 1 Flow chart of study participants

SAH patients admitted to ICU or IMC from 09/2018 to 09/2019: n=77

Immediate withdrawal of care: n=5
Lack of assessment of autonomic cardiovascular modulation within 24 hours after symptom onset: n=19
CAA or trauma as primary cause of SAH: n=2

Assessment of autonomic cardiovascular modulation in patients with spontaneous SAH within 24 hours after symptom onset: n=51

SAH patients with Hunt and Hess grade < 3 upon admission: n=19
SAH patients with Hunt and Hess grade ≥ 3 upon admission: n=32

SAH patients with H&H grade 1: n=14
SAH patients with H&H grade 2: n=5
SAH patients with H&H grade 3: n=12
SAH patients with H&H grade 4: n=11
SAH patients with H&H grade 5: n=9

Outcome Measures:
Identification of parameters of autonomic cardiovascular dysfunction in SAH patients compared to 20 healthy volunteers
Associations between disease severity and autonomic dysfunction
Associations between autonomic cardiovascular modulation and functional outcome at discharge
Table 1 Baseline and clinical characteristics of 51 patients with spontaneous subarachnoid hemorrhage according to clinical disease severity, either Hunt-and-Hess score < 3 or ≥ 3

| Parameter | SAH patients (n = 51) | Hunt & Hess < 3 (n = 19) | Hunt & Hess ≥ 3 (n = 32) | p value |
|-----------|-----------------------|--------------------------|--------------------------|---------|
| Age in years, median (IQR) | 54 (50–63) | 50 (43–57) | 58.5 (51.5–66.5) | 0.006* |
| Women, n (%) | 27 (52.9%) | 8 (42.1%) | 19 (59.4%) | 0.232 |
| Prior comorbidities, n (%) | | | | |
| Arterial hypertension | 26 (51%) | 8 (42.1%) | 18 (56%) | 0.329 |
| Diabetes mellitus | 8 (15.7%) | 3 (15.8%) | 5 (15.6%) | 0.640 |
| Dyslipidemia | 8 (15.7%) | 3 (15.8%) | 5 (15.6%) | 0.640 |
| Prior ischemic stroke/TIA | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Status post endovascular treatment | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Congestive heart failure | 4 (7.8%) | 1 (5.3%) | 3 (9.4%) | 0.521 |
| Smoker | 10 (19.6%) | 4 (21.1%) | 6 (18.8%) | 0.557 |
| Alcohol abuse | 3 (5.9%) | 1 (5.3%) | 2 (6.3%) | 0.691 |
| Premedication, n (%) | | | | |
| Antiplatelet drug (ASA, clopidogrel) | 6 (11.8%) | 2 (10.5%) | 4 (12.5%) | 0.604 |
| Oral anticoagulant (phenprocoumon) | 2 (3.9%) | 0 (0%) | 2 (6.3%) | 0.523 |
| Antihypertensive drug | 16 (31.4%) | 5 (26.3%) | 11 (34.4%) | 0.549 |
| Pre-mRS, median (Range) | 0 (3) | 0 (0) | 0 (3) | 0.030* |
| Admission status, median (IQR) | | | | |
| Heart rate, min⁻¹ | 66.6 (60.1–80.9) | 71.7 (64.4–77.7) | 64.8 (57.3–81.4) | 0.349 |
| Systolic blood pressure, mmHg | 130.1 (116.2–144.5) | 138.8 (120.4–155.8) | 127.2 (111.7–142.5) | 0.06 |
| Parameters of SAH on CT scan, n (%) | | | | |
| Detection of SAH on CT scan | 50 (98%) | 18 (94.7%) | 32 (100%) | 0.373 |
| Detection of SAH only in CSF | 1 (2%) | 1 (5.3%) | 0 (0%) | 0.373 |
| Detection of aneurysm | 37 (72.5%) | 12 (63.2%) | 25 (78.1%) | 0.247 |
| Anterior circulation | 27 (52.9%) | 10 (52.6%) | 17 (53.1%) | 0.888 |
| Ant. comm. artery (ACOM) | 16 (31.4%) | 8 (42.1%) | 8 (25%) | 0.203 |
| Middle cerebral artery (MCA) | 5 (9.8%) | 1 (5.3%) | 4 (12.5%) | 0.639 |
| Pericallosal artery | 1 (2.0%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Internal carotid artery (ICA) | 5 (9.8%) | 1 (5.3%) | 4 (12.5%) | 0.639 |
| Posterior circulation | 10 (19.6%) | 2 (10.5%) | 8 (25%) | 0.287 |
| Post. comm. artery (PCOM) | 4 (7.8%) | 1 (5.3%) | 3 (9.4%) | 0.521 |
| Basilar artery (BA) | 3 (5.9%) | 0 (0%) | 3 (9.4%) | 0.285 |
| Ant. inf. cerebellar artery (AICA) | 1 (2%) | 1 (5.3%) | 0 (0%) | 0.373 |
| Post. inf. cerebellar artery (PICA) | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Vertebral artery (VA) | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Other sources of bleeding | 3 (5.9%) | 1 (5.3%) | 2 (6.3%) | 0.691 |
| Dysplasia of internal carotid artery (ICA) | 1 (2%) | 1 (5.3%) | 0 (0%) | 0.373 |
| Dissection of basilar artery (BA) | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Arteriovenous fistula in cervical spine | 1 (2%) | 0 (0%) | 1 (3.1%) | 0.627 |
| Intracerebral hemorrhage | 13 (25.5%) | 2 (10.5%) | 11 (34.4%) | 0.056 |
| Left hemisphere | 6 (11.8%) | 1 (5.3%) | 5 (15.6%) | 0.392 |
| Right hemisphere | 6 (11.8%) | 0 (0%) | 6 (18.8%) | 0.050 |
| Corpus callosum | 1 (2%) | 1 (5.3%) | 0 (0%) | 0.331 |
| Intraventricular hemorrhage | 30 (58.8%) | 6 (31.6%) | 24 (75%) | 0.002* |
| Acute occluding hydrocephalus | 30 (58.8%) | 5 (26.3%) | 25 (78.1%) | <0.001* |
| Parameters during first measurement, n (%) | | | | |
| Intubated patient | 30 (58.8%) | 2 (10.5%) | 28 (87.5%) | <0.001* |
| Catecholamines (norepinephrine) | 21 (41.2%) | 1 (5.3%) | 20 (62.5%) | <0.001* |
| Sedation | 29 (56.9%) | 2 (10.5%) | 27 (84.4%) | <0.001* |
| External ventricular drain | 29 (56.9%) | 5 (26.3%) | 24 (75.0%) | 0.001* |
| mRS at discharge, Median (IQR) | 2 (0–5) | 0 (0–1) | 4 (1–5) | <0.001* |

SAH subarachnoid hemorrhage, n number, IQR interquartile range, TIA transient ischemic attack, ASA acetylsalicylic acid, SD standard deviation, pre-mRS modified Rankin Scale before ictus, min⁻¹ per minute, mmHg millimeter of mercury, CT computed tomography, CSF cerebrospinal fluid.
Statistical analysis

For data analysis, we used a commercially available statistical program (IBM SPSS Statistics for Windows, version 24). Significance was set at $p < 0.05$. Testing for normal distribution was performed using the Kolmogorov–Smirnov test. Data are expressed as median and interquartile range. Normally distributed patient and control data were compared using the $t$ test for unpaired samples and the Mann–Whitney–U test for comparison of non-normally distributed data.

For subgroup analysis, we categorized patients according to their clinical condition into two groups: H&H-scores 1–2 (H&H < 3; no neurological deficit other than cranial nerve palsy) and H&H-scores 3–5 (H&H ≥ 3; altered level of consciousness and neurological deficits). As age-dependent normative values had only been determined for time-domain parameters, we chose RRI-CV as a parameter of total autonomic cardiovascular modulation to further dichotomize our patient cohort [10]. Therefore, another subgroup analysis was carried out by assessing associations between normal vs pathological RRI-CV and the mRS at discharge, Fig. 3).

Correlations between H&H-scores, all bio-signals as well as autonomic cardiovascular parameters were assessed using Spearman rank correlation. Receiver-operating-characteristic (ROC) analysis was performed to investigate associations of H&H-scores with autonomic cardiovascular modulation and to determine the best cut-off values for prediction of H&H ≥ 3. To adjust for possible baseline confounders, multivariate analyses (binary logistic regression) were adjusted for established parameters—age, pre-mRS, IVH, and intubation—i.e., parameters identified to be associated with initial clinical severity according to H&H-scores in univariate analyses (Table 1).

Results

Over a 12 month period, a total of 77 patients with SAH were screened for eligibility (Fig. 1). After exclusion of patients with immediate withdrawal of care due to unfavourable prognosis, lack of assessment of autonomic cardiovascular modulation within 24 h after symptom onset, and cerebral Amyloid angiopathy or trauma as primary cause of SAH, 51 patients (H&H < 3; n = 19, H&H ≥ 3; n = 32) were enrolled in the study (27 women, 24 men; 54.0 (50.0–63.0) years). Clinical baseline characteristics of patients and controls are presented in Tables 1 and 2. Patients with higher H&H-scores were significantly older than patients with lower H&H-scores ($p = 0.005$), as well as controls ($p < 0.001$). Although patients with higher H&H-scores had a slightly though significantly higher pre-mRS than patients with lower H&H-scores [Median (Range), 0 (3) vs 0 (0); $p = 0.030$], both groups did not differ regarding prior cardio- and cerebrovascular comorbidities and premedication (Table 1, Suppl-Table 1). Most radiological parameters of SAH on admission CT-scans did not differ between both groups, yet patients with higher H&H-scores had higher incidences of occluding hydrocephalus, concomitant parenchymal, and intraventricular hemorrhage. Moreover, during the first 24 h after symptom onset, acute intensive care interventions (i.e., mechanical ventilation, use of analgo-sedation, vasopressor therapy, or CSF drainage via EVD) were significantly more often required in patients with higher H&H-scores (Table 1).

Parameters of cardiovascular autonomic modulation: SAH patients vs controls

Overall, between SAH patients and controls, there were no significant differences in the assessed bio-signals used for further analysis of autonomic modulation, i.e., RRIs and SBP (Table 2). Parameters reflecting sympathetic cardiac modulation, i.e., RRI-LF-powers and SBP-LF-powers were significantly lower in SAH patients than in controls. Similarly, patients had significantly lower values of parameters of total autonomic modulation, i.e., RRI-total powers, RRI-SD, RRI-CV, as well as RRI-LF/HF-ratios as an index of sympatho-vagal balance (Table 2). In contrast, parameters of vagal cardiac modulation did not differ between patients and controls.

Subgroup analyses of parameters of cardiovascular autonomic modulation: patients with H&H < 3 vs controls and patients with H&H ≥ 3 vs controls

In a next step, we compared parameters of cardiovascular autonomic modulation between patients with lower and higher H&H-scores to those of healthy controls. While parameters reflecting sympathetic (RRI-LF-powers, SBP-LF-powers), parasympathetic (RRI-HF-powers), and total autonomic modulation (RRI-total powers, RRI-SD, RRI-CV) only showed a trend towards lower values in patients with lower H&H-scores compared to controls, these differences reached statistical significance when comparing patients with higher H&H-scores to healthy controls (Table 2). Only RRI-LF/HF-ratios as an index of...
sympatho-vagal-balance were significantly lower in both patient subgroups than in controls (Table 2).

**Subgroup analyses of parameters of cardiovascular autonomic modulation: patients with H&H < 3 vs H&H ≥ 3**

To investigate possible associations between cardiovascular autonomic modulation and clinical SAH severity, we compared parameters between patients with lower and higher H&H-scores (Table 2). With increasing SAH severity, subgroup analyses revealed a decrease of parameters reflecting sympathetic cardiac modulation (RRI-LF-powers, SBP-LF-powers), total autonomic modulation (RRI-total powers, RRI-SD, RRI-CV), as well as sympatho-vagal-balance (RRI-LF/HF-ratios). The parameters RRI-RMSSD and RRI-HF-powers, reflecting vagal cardiovascular outflow, only showed a trend towards lower values in patients with higher compared to patients with lower H&H-scores ($p > 0.05$; Table 2).

**Associations between parameters of cardiovascular autonomic modulation and SAH severity**

There was no significant correlation between H&H-scores and RRI s or parameters of vagal cardiac modulation (RRI-RMSSD and RRI-HF-powers). In contrast, SAH severity correlated inversely and significantly with SBP (Rho = −0.291, $p = 0.047$), indices of sympathetic cardiovascular modulation, i.e., RRI-LF-powers (Rho = −0.524, $p < 0.001$) and SBP-LF-powers (Rho = −0.560, $p < 0.001$), total autonomic modulation, i.e., RRI-total powers (Rho = −0.532, $p < 0.001$), RRI-SD (Rho = −0.434, $p = 0.003$), and RRI-CV (Rho = −0.519, $p < 0.001$), as well as sympatho-vagal-balance, i.e., RRI-LF/HF-ratios (Rho = −0.484, $p = 0.001$; Fig. 2).

In a next step, we calculated cut-off values of autonomic cardiovascular parameters best discriminative for H&H ≥ 3. All parameters of sympathetic modulation, total autonomic modulation, and sympatho-vagal balance showed significant associations with SAH severity [AUC (95%CI): RRI-LF-powers 0.800 (0.666–0.933), $p = 0.001$; SBP-LF-powers 0.846 (0.725–0.967), $p < 0.001$; RRI-total powers 0.825 (0.697–0.952), $p < 0.001$; RRI-SD 0.746 (0.602–0.890), $p = 0.005$; RRI Variance 0.810 (0.688–0.932), $p < 0.001$; RRI-LF/HF-ratios 0.767 (0.604–0.930), $p = 0.003$], while there were no significant associations between parameters of parasympathetic modulation and SAH severity [AUC (95%CI): RRI-HF-powers 0.637 (0.460–0.814), $p = 0.145$; RRI-RMSSD 0.633 (0.470–0.797), $p = 0.12$].

Given possible influences of differences in baseline and clinical characteristics on autonomic cardiovascular modulation, we performed multivariate analyses corrected for confounding variables to verify associations of autonomic cardiovascular dysfunction and clinical SAH severity (Table 3). The exploratory results of these multivariate analyses did not reveal significant associations between autonomic cardiovascular modulation and age, pre-mRS, intraventricular hemorrhage, and intubation ($p > 0.050$ for all possible variables confounding the assessed parameters of autonomic cardiovascular modulation).

In contrast, we identified clinical SAH severity as independent variable for impaired autonomic sympathetic cardiovascular modulation [RRI-LF: OR 9.20 (1.20–70.48), $p = 0.033$; SBP-LF: OR 47.95 (1.96–1173.02), $p = 0.018$] and parameters of total autonomic cardiovascular modulation [RRI-SD: OR 12.49 (1.34–116.65), $p = 0.027$; RRI-CV: OR 12.16 (1.13–131.50), $p = 0.040$; Table 3].

**Prognostic value of cardiovascular autonomic parameters for clinical outcome in SAH patients**

To investigate possible associations between parameters of autonomic cardiovascular modulation within 24 h after symptom onset and short-term clinical SAH outcome at discharge, we additionally performed subgroup analyses using RRI-CV as a parameter of total autonomic cardiovascular modulation with established age-dependant normative values. Dichotomisation of our patient cohort into the two groups non-pathological ($n = 34$) vs pathological ($n = 17$) RRI-CV revealed clear associations between impaired autonomic cardiovascular modulation within 24 h after SAH onset and functional outcome at discharge (Fig. 3). Thus, patients with impaired cardiovascular autonomic modulation had significantly higher rates of unfavourable outcome at discharge compared to patients with normal RRI-CV (Fig. 3).

**Discussion**

To the best of our knowledge, this is the first observational study prospectively assessing a possible impairment of autonomic cardiovascular modulation in SAH patients in association with clinical severity during the acute phase after symptom onset. In our patients, we were able to demonstrate an inverse correlation between parameters of sympathetic and total autonomic cardiovascular modulation and H&H-scores, i.e., an increasing reduction of autonomic cardiovascular modulation with higher H&H-scores independent of potential confounding variables like age, mechanical ventilation, and co-medication.

In general, previous trials have controversially discussed possible influences of SAH on the central autonomic control. In contrast to our findings in SAH patients, animal trials described an increase in sympathetic activity
and BP modulation accompanied by a distinct release of plasma catecholamines within the first hours after experimentally induced SAH [12, 13]. In clinical trials, sympathetic overexcitation has been described within the first few days after ictus and suggested to be responsible for multiple systemic complications like neurogenic pulmonary edema or myocardial contraction band necrosis [2, 14]. In contrast, other authors described a loss of parasympathetic activity within the first few days after SAH and suggested an association between lower values of vagal cardiovascular modulation and life-threatening secondary complications, i.e., cerebral vasospams, delayed cerebral ischemia, and sepsis [15, 16]. Finally, some trials postulated a combined dysfunction with augmented vagal and sympathetic activity within the first days after SAH [17].
Despite these contradictory findings, acute focal parenchymal brain lesions, e.g., due to ischemic stroke especially with insular cortical damage, but also traumatic brain injury, have been postulated to induce a decrease of total autonomic modulation with a shift towards sympathetic predominance [1, 4, 18, 19]. A possible explanation for this may be the different underlying pathophysiology of brain injury caused by these diseases, i.e., a focal parenchymal lesion with a consecutive dysfunction of central autonomic network structures, including supratentorial and infratentorial areas (“brain–heart axis”) [1].

In contrast to observations in patients with focal brain lesions, the decrease of total and sympathetic autonomic modulation of our patients may be explained by a diffuse

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**Table 2** Biosignals and parameters of autonomic cardiovascular modulation of 51 SAH patients, Hunt & Hess < 3 (n = 20) and Hunt & Hess ≥ 3 (n = 19) and 20 healthy controls

| Parameter, median (IQR) | SAH patients (n = 51) | Healthy controls (n = 20) | Hunt & Hess < 3 (n = 19) | Hunt & Hess ≥ 3 (n = 32) | p value | p value | p value | p value |
|--------------------------|-----------------------|--------------------------|--------------------------|--------------------------|---------|---------|---------|---------|
| Age, years | 54.0 (50.0–63.0) | 50.0 (37.5–55.8) | 50.0 (43.0–57.0) | 58.5 (51.5–66.5) | 0.002<sup>b,c</sup> | 0.258<sup>c</sup> | <0.001<sup>a,b</sup> | 0.005<sup>b,c</sup> |
| Sex (women), n (%) | 27 (52.9%) | 11 (55.0%) | 8 (42.1%) | 19 (59.4%) | 0.888 | 0.420 | 0.752 | 0.232 |
| Biosignals | | | | | | | | |
| RRI mean, ms | 886.0 (739.3–995.7) | 754.1 (728.7–926.9) | 859.0 (752.0–940.1) | 908.1 (735.1–1042.8) | 0.185<sup>a</sup> | 0.706<sup>c</sup> | 0.181<sup>c</sup> | 0.349<sup>c</sup> |
| SBP mean, mmHg | 130.1 (116.2–144.5) | 128.4 (122.2–139.0) | 138.8 (120.4–155.8) | 127.2 (111.7–142.5) | 0.347<sup>c</sup> | 0.081<sup>c</sup> | 0.853<sup>c</sup> | 0.060<sup>c</sup> |
| Parameters of sympathetic modulation | | | | | | | | |
| RRI-LF-powers, ms<sup>2</sup> | 141.0 (18.9–402.4) | 442.3 (246.8–921.2) | 338.6 (179.7–710.4) | 72.1 (10.1–175.9) | 0.001<sup>a,b</sup> | 0.317<sup>c</sup> | <0.001<sup>a,b</sup> | 0.001<sup>a,b</sup> |
| SBP-LF-powers, mmHg<sup>2</sup> | 3.4 (1.3–11.0) | 14.5 (7.8–20.4) | 11.0 (4.7–17.0) | 1.6 (0.9–5.5) | <0.001<sup>a,b</sup> | 0.131<sup>c</sup> | <0.001<sup>a,b</sup> | <0.001<sup>a,b</sup> |
| Parameters of parasympathetic modulation | | | | | | | | |
| RRI-RMSSD, ms | 17.9 (11.8–36.5) | 20.6 (14.2–28.3) | 26.0 (14.7–40.1) | 15.9 (9.9–30.2) | 0.279<sup>c</sup> | 0.103<sup>c</sup> | 0.856<sup>c</sup> | 0.171<sup>c</sup> |
| RRI-HF-powers, ms<sup>2</sup> | 77.2 (18.7–128.8) | 145.3 (32.0–258.2) | 97.7 (19.1–311.9) | 73.8 (13.1–103.9) | 0.114<sup>c</sup> | 0.710<sup>c</sup> | 0.041<sup>b,c</sup> | 0.151<sup>c</sup> |
| Parameters of total autonomic modulation | | | | | | | | |
| RRI-total powers, ms<sup>2</sup> | 207.1 (78.4–540.7) | 624.0 (353.9–1588.6) | 562.5 (282.5–1566.5) | 115.5 (21.6–230.2) | 0.001<sup>a,b</sup> | 0.608<sup>c</sup> | <0.001<sup>a,b</sup> | <0.001<sup>a,b</sup> |
| RRI-SD, ms | 20.6 (10.7–31.1) | 30.4 (23.2–45.9) | 28.4 (19.7–40.2) | 15.0 (9.3–25.5) | 0.011<sup>a,b</sup> | 0.530<sup>c</sup> | 0.001<sup>a,b</sup> | 0.010<sup>b,c</sup> |
| RRI-CV, % | 2.4 (1.2–3.7) | 3.7 (3.1–5.3) | 3.5 (2.3–5.4) | 1.6 (1.0–2.8) | 0.002<sup>a,b</sup> | 0.499<sup>c</sup> | <0.001<sup>a,b</sup> | <0.001<sup>a,b</sup> |
| Index of sympatho-vagal-balance | | | | | | | | |
| RRI-LF/HF-ratios | 1.1 (0.7–1.9) | 4.0 (1.7–10.0) | 2.1 (0.9–3.2) | 0.9 (0.6–1.5) | <0.001<sup>a,b</sup> | 0.005<sup>b,c</sup> | <0.001<sup>a,b</sup> | 0.003<sup>a,b</sup> |

**SAH** subarachnoid hemorrhage, n number, H&H Hunt-and-Hess score, Pat patients, Ct healthy controls, RRI R–R interval, SBP systolic blood pressure, LF low frequency, HF high frequency, RMSSD root mean square of successive differences, ms milliseconds, mmHg millimeter of mercury, SD standard deviation, CV coefficient of variance

<sup>a</sup>p values derived from the nonparametric Mann–Whitney-test

<sup>b</sup>significant differences between patients and controls

<sup>c</sup>p values derived from t tests
disruption of autonomic network structures. After SAH, pathophysiological processes induce a rapid endocrine stress response through the hypothalamic–pituitary–adrenal axis [1]. These dynamic changes have been described in animal trials, where sympathoexcitation with increasing levels of serum cortisol, aldosterone, and catecholamines in the hyperacute phase after experimentally induced SAH was observed [12, 13]. Although no data exist for these very early changes in humans, a sympathetic storm caused by a massive meningeal pain stimulus through blood in the cerebrospinal fluid (CSF) space and an increased ICP seems a plausible explanation for increased catecholamine levels in the CSF and plasma of SAH patients [1, 2, 20].

In line with the results of Kawahara et al. and Levy et al., we hypothesize that a possible initial sympathetic storm with elevated catecholamines may trigger a negative feedback mechanism to cardiogenic centres in the brainstem, suppressing the sympathetic influence on the sinus cycle of the heart [17, 21, 22]. Thus, our results of decreased sympathetic autonomic modulation within 24 h after symptom onset may be explained by such feedback mechanisms after the initial catecholamine release. Furthermore, blood induced meningeal affection may trigger the trigemino-cardiac reflex via mechanoreceptors activating the motor nucleus of the vagus nerve. Hence, pain-induced stimulation of the hypothalamus may induce vagal activation and further buffer sympathetic outflow [20, 23, 24].

In conclusion, we assume that the initial meningeal pain stimulus and increasing ICP may induce sympathetic overexcitation and catecholamine release immediately after SAH onset. While brain parenchyma and therefore ANS network structures are not directly affected, various mechanisms, i.e., negative feedback to the vagi and the trigemino-cardiac reflex may buffer the negative effects of the initial sympathetic storm. This counter regulation seems to depend on clinical severity as we have observed decreasing values of the index of sympatho-vagal balance (RRI-LF/HF-ratios) with higher H&H-scores (Table 2, Fig. 2).

Overall, we cannot rule out an influence of differences in baseline and clinical characteristics or co-medication on our findings. General anaesthesia has previously been associated with decreased HRV [25, 26], and the influence of opioids on the ANS is complex [27]. Furthermore, catecholamines as the predominantly used vasopressors to maintain SBP in critically ill patients induce tachycardia and decrease time-domain measures of HRV, i.e., RRI-SD and RRI-RMSSD [28, 29]. Yet, multivariable regression analyses corrected for confounding variables verified the association of autonomic cardiovascular dysfunction and clinical SAH severity in our cohort, and parameters identified to be associated with initial clinical severity according to H&H, i.e., age, pre-mRS, IVH, and intubation, were not significantly associated with autonomic cardiovascular modulation using multiple logistic regression (Table 3). These statistical tests only represent an approach to estimate the extent of possible confounding parameters and procedures. Although our results suggest
that differences in baseline and clinical characteristics or the use of concomitant medication for vasopressor therapy and analgo-sedation may at the most to some extend explain the decrease in HRV observed in all our patients, significance of these results is limited due to the small sample size.

As mentioned above, a reduction of HRV in critically ill patients is associated with a higher risk of cardiovascular events and poor clinical outcome. Yet, the question remains whether autonomic dysfunction in the acute phase of spontaneous SAH may influence clinical outcome. When applying established age-dependant normative values to dichotomize the patient cohort into the two subgroups normal vs impaired autonomic cardiovascular modulation, our results demonstrated significantly higher rates of unfavourable short-term outcome (i.e., mRS at discharge) in patients with autonomic impairment upon testing within 24 h after SAH onset. Although no clear utility for clinical practice can be derived from these findings, our results suggest that the severity of the impairment of autonomic modulation already in the acute phase of SAH may be associated with clinical outcome and possibly a higher risk for severe secondary complications, i.e., arrhythmias, cerebral vasospasm, neurogenic pulmonary edema, or sepsis. Yet, as mRS at discharge may not represent a suitable surrogate measure for functional outcome after SAH, further studies are needed before results may be generalized for clinical utilization.

Despite several strengths and the novelty of our results, some limitations may undermine generality of our study. First, the sample size of our patient group may still have been too small to establish valid predictors for patients at risk of secondary complications after SAH. Defined exclusion criteria only comprised (I) immediate withdrawal of care, (II) lack of assessment of autonomic cardiovascular modulation within 24 h after symptom onset, and (III) cerebral Amyloid angiopathy or trauma as primary cause of SAH to not further minimize our cohort. Thus, the cohort is rather heterogeneous regarding other parameters potentially influencing autonomic cardiovascular modulation, which might limit generalizability of our results. Therefore, some uncertainty remains to interpret the explanatory results of the multivariate analyses considering the imbalance between the small sample size and possible clinical and radiological confounders such as usage of antihypertensive medication or influence of intracranial pressure. Furthermore, we were not able to stratify according to radiological parameters of SAH. Acute occluding hydrocephalus, concomitant parenchymal and intraventricular hemorrhage may vary in their susceptibility in altering autonomic function. We did not correlate autonomic impairment with long-term clinical outcomes after SAH and the mRS at discharge may not be a suitable surrogate parameter for outcome prognostication after SAH. So far, the utility of autonomic monitoring in clinical practice remains unclear. Our findings of an increasing reduction of autonomic cardiovascular modulation with higher H&H-scores during the acute phase after symptom onset encourage follow-up assessments to determine the

![Modified Rankin Scale (mRS) at discharge](image)

**Fig. 3** RRI-CV as a parameter of total autonomic cardiovascular modulation in relation to disease severity
duration and time course of autonomic dysfunction after SAH. Although possible autonomic perturbations might contribute to or deteriorate secondary complications after SAH, further investigations assessing possible changes of autonomic modulation during the course of in-hospital treatment are needed to clarify whether this approach may reliably predict clinical outcome. Finally, we chose a healthy control group with no known comorbidities and no medication to assure as few confounding factors on the autonomic nervous system modulation as possible. Yet, a second control group—matched for comorbidities and previous medication—would add valuable information in the field of autonomic nervous system research and this aspect should be addressed in follow-up studies.

**Conclusion**

In conclusion, within 24 h after SAH, our results show a decline of sympathetic and total autonomic cardiovascular modulation, which might be ascribed to various mechanisms buffering the initial meningeal pain stimulation and ICP elevation. Finally, short-term functional outcome seems to be associated with the severity of autonomic impairment upon hospital admission.

Further studies need to verify these findings to identify whether early autonomic dysfunction may predict complications and influence decision making in SAH patients.

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**Author contribution** All authors contributed to the study conception and design. MCB and JK researched literature and conceived the study. PH, TE, and AD were involved in analysis and interpretation of data. STG and PM were involved in drafting of the manuscript. HBH, JBK, and SS were revising the manuscript for intellectual content. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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**Data availability** Data may be shared by writing to the corresponding author.

**Declarations**

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This study has been approved by the ethics committee of the University of Erlangen-Nuremberg and had therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** Written informed consent has been obtained from all study participants or their legal representatives for the patient’s anonymized information to be published in this article.

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**References**

1. Manea MM et al (2015) Brain-heart axis—review article. J Med Life 8(3):266–271
2. Garg R, Bar B (2017) Systemic complications following aneurysmal subarachnoid hemorrhage. Curr Neurol Neurosci Rep 17(1):7
3. Feigin VL et al (2021) Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 20(10):795–820
4. Hilz MJ et al (2011) High NIMHSS values predict impairment of cardiovascular autonomic control. Stroke 42(6):1528–1533
5. Long B, Koyfman A, Runyon MS (2017) Subarachnoid hemorrhage: updates in diagnosis and management. Emerg Med Clin North Am 35(4):803–824
6. van Gijn J et al (1985) Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg 63(3):355–362
7. Bogert LW, van Lieshout JJ (2005) Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. Exp Physiol 90(4):437–446
8. Friedrich C et al (2010) Baroreflex sensitivity and power spectral analysis during autonomic testing in different extrapyramidal syndromes. Mov Disord 25(3):315–324
9. Hilz MJ (2002) Quantitative autonomic functional testing in clinical trials. In: Neuromuscular function and disease. In: Brown WF, Bolton CF, Aminoff MJ (eds) Basic, clinical and electrodiagnostic aspects. W.B. Sanders Company, Philadelphia, pp 1899–1929
10. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of pacing and electrophysiology. Circulation 93(5):1043–1065
11. Rudiger H, Klinghammer L, Schueck K (1999) The trigonometric regressive spectral analysis—a method for mapping of beat-to-beat recorded cardiovascular parameters on to frequency domain in comparison with Fourier transformation. Comput Methods Programs Biomed 58(1):1–15
12. Lambert E et al (2000) Subarachnoid hemorrhage induced sympathoexcitation arises due to changes in endothelin and/or nitric oxide activity. Cardiovasc Res 45(4):1046–1053
13. Nyberg C et al (2016) The early endocrine stress response in experimental subarachnoid hemorrhage. PLoS One 11(3):e0151457
14. Su IC et al (2009) Prediction of early secondary complications in patients with spontaneous subarachnoid hemorrhage based on accelerated sympathovagal ratios. Acta Neurochir (Wien) 151(12):1631–1637
15. Schmidt JM et al (2014) Heart rate variability for preclinical detection of secondary complications after subarachnoid hemorrhage. Neurocrit Care 20(3):382–389
16. Schmidt JM (2016) Heart rate variability for the early detection of delayed cerebral ischemia. J Clin Neurophysiol 33(3):268–274
17. Kawahara E et al (2003) Role of autonomic nervous dysfunction in electrocardiographic abnormalities and cardiac injury in patients with acute subarachnoid hemorrhage. Circ J 67(9):753–756
18. Khalid F et al (2019) Autonomic dysfunction following traumatic brain injury: translational insights. Neurosurg Focus 47(5):E8
19. Rabinstein AA (2007) Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. Neurol Res 29(7):680–682
20. Prasad Hrishi A, Ruby Lionel K, Prathapadas U (2019) Head Rules over the heart: cardiac manifestations of cerebral disorders. Indian J Crit Care Med. 23(7):329–335
21. Levy MN, Zieske H (1969) Autonomic control of cardiac pacemaker activity and atrioventricular transmission. J Appl Physiol 27(4):465–470
22. Breuer HW et al (1993) Heart rate variability and circulating catecholamine concentrations during steady state exercise in healthy volunteers. Br Heart J 70(2):144–149
23. Chowdhury T, Schaller B (2016) The role of acute trigemino-cardiac reflex in unusual, non-surgical cases: a review. Front Neurol 7:186
24. Lv X, Wu Z, Li Y (2014) Innervation of the cerebral dura mater. Neuroradiol J 27(3):293–298
25. Matchett G, Wood P (2014) General anesthesia suppresses normal heart rate variability in humans. Chaos 24(2):023129
26. Haberthur C, Lehmann F, Ritz R (1996) Assessment of depth of midazolam sedation using objective parameters. Intensive Care Med 22(12):1385–1390
27. Egan TD (2019) Are opioids indispensable for general anaesthesia? Br J Anaesth 122(6):e127–e135
28. Ahmed MW et al (1994) Effect of physiologic and pharmacologic adrenergic stimulation on heart rate variability. J Am Coll Cardiol 24(4):1082–1090
29. Goldberger JJ et al (1994) Dissociation of heart rate variability from parasympathetic tone. Am J Physiol 266(5 Pt 2):H2152–H2157