Journal of Critical Care 72 (2022) 154123

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

NT-proBNP and troponin I in high-grade aneurysmal subarachnoid hemorrhage: Relation to clinical course and outcome

Teodor Svedung Wettervik, MD PhD *, Timothy Howells, PhD, Anders Hånell, PhD, Christoffer Nyberg, MD PhD, Elisabeth Ronne-Engström, MD PhD

Department of Neuroscience, Section of Neurosurgery, Uppsala University, SE-751 85 Uppsala, Sweden

ARTICLE INFO

Keywords:
Aneurysmal subarachnoid hemorrhage
Cerebral pressure autoregulation
Intracranial pressure
Neurointensive care
NT-proBNP
Troponin I

ABSTRACT

Purpose: To investigate the association between two cardiac biomarkers, NT-proBNP and TnI, with intracranial pressure (ICP)—/cerebral perfusion pressure (CPP)-insults, cerebral pressure autoregulation, delayed ischemic neurological deficits (DIND), and clinical outcome after aneurysmal subarachnoid hemorrhage (aSAH).
Methods: In this retrospective study, 196 aSAH patients treated at the neurointensive care unit, Uppsala University Hospital, Sweden, 2011–2018, with ICP-monitoring and serial NT-proBNP and TnI measurements were included. The first 10 days were divided into early phase (day 1–3) and vasospasm phase (day 4–10).
Results: NT-proBNP and TnI were elevated above the reference interval at least once the first 10 days in 175 (89%) and 116 (59%) patients, respectively. In the vasospasm phase, higher NT-proBNP and TnI were associated with increased percentage of CPP below 60 mmHg. Higher TnI also correlated with more ICP-insults above 20 mmHg. NT-proBNP and TnI did not predict worse pressure autoregulation and DIND. Higher NT-proBNP and TnI were associated with mortality and unfavorable outcome in univariate, but not multivariate, analyses.
Conclusion: Elevated NT-proBNP and TnI correlated with an increased burden of secondary ICP-/CPP-insults, but not with worse pressure autoregulation, DIND, and without independent association with clinical outcome.

1. Introduction

Rupture of an intracranial aneurysm leads to a subarachnoid hemorrhage (aSAH), a severe brain injury associated with poor clinical outcome [1]. Current management aims to reduce cerebral complications, by early aneurysm occlusion to prevent re-bleeding, external ventricular drain (EVD) to relieve acute hydrocephalus, and prevention, detection, and early treatment of delayed ischemic neurological deficits (DIND) [2].

In addition to cerebral complications, aSAH often elicits a severe systemic stress response with increased hypothalamic-pituitary axis (HPA)-[3] and sympathetic activity [4]. This may cause secondary systemic organ injury. Specifically, secondary cardiac dysfunction, including arrhythmias and stress-induced cardiomyopathy (SIC), is common and may lead to cardiac arrest, hemodynamic instability, and cerebral hypoperfusion [4,5]. Previous studies support that aSAH-induced cardiac failure increases the risk for arterial hypotension [6], DIND and brain infarction [6,7], unfavorable clinical outcome [7], and mortality [7]. Consequently, there is an increased interest in monitoring the extent of cardiac dysfunction and blood biomarkers including brain natriuretic protein (BNP) and troponin. These biomarkers are nowadays routinely measured after aSAH. BNP was initially found in the brain, but is more likely released by the cardiac ventricles in response to fluid load. Prohormone of BNP is cleaved into BNP and the inactive N-terminal prohormone of BNP (NT-pro-BNP). BNP and NT-proBNP are comparable biomarkers for cardiac failure, but NT-proBNP is considered to be more stable thanks to a longer half-life [8]. Troponin is released by cardiomyocytes in response to damage and indicates cardiac injury. Pathological increases in both of these biomarkers are common after aSAH and are associated with a more severe neurological injury at admission [9-12] and development of cardiac dysfunction [5,11] and cerebral complications such as vasospasm [13], DIND [12-16], brain infarction [6,17], and poor clinical outcome [11,12,16,18]. However, it is

Abbreviations: ABP, Arterial blood pressure; aSAH, Aneurysmal subarachnoid hemorrhage; BNP, Brain natriuretic protein; CPP, Cerebral perfusion pressure; CSF, Cerebrospinal fluid; DIND, Delayed ischemic neurological deficits; EVD, External ventricular drainage; GCS M, Glasgow Coma Scale Motor score; HHH-therapy, Hypertension, hypervolemia, and hemodilution therapy; HPA, Hypothalacic-pituitary axis; GOS-E, Glasgow outcome scale-extended; ICP, Intracranial pressure; MAP, Mean arterial blood pressure; NIC, Neurointensive care; NT-proBNP, N-terminal prohormone of BNP; PRx, Pressure reactivity index; sBP, Systolic blood pressure; SIC, Stress-induced cardiomyopathy; TnI, Troponin I; WFNS, World Federation of Neurosurgical Societies.

* Corresponding author.
E-mail address: teodor.svedung-wettervik@neuro.uu.se (T. Svedung Wettervik).

https://doi.org/10.1016/j.jcrc.2022.154123

not fully clear to what extent the association with cerebral complications is explained by a worse underlying primary brain injury or from secondary brain injury due to e.g. hemodynamic disturbances from cardiac dysfunction.

In the current study, the primary aim was to study the temporal dynamics of the two cardiac biomarkers NT-proBNP (associated with cardiac failure) and troponin I (TnI; associated with cardiac injury) in relation to the burden of secondary insults, including intracranial pressure (ICP)- and cerebral perfusion pressure (CPP)-insults, and cerebral pressure autoregulatory disturbances. The secondary aim was to study the relation of NT-proBNP and TnI to the development of DIND and long-term clinical outcome.

2. Materials and methods

2.1. Patients

Patients with aSAH admitted to the Department of Neurosurgery at the University Hospital in Uppsala, Sweden, 2011–2018 were eligible for this study. Out of 327 patients with aSAH and ICP monitoring, 196 patients aged 16 or older, who received ICP-monitoring, and with available lab data of NT-proBNP in both the early phase (day 1–3) and the vasospasm phase (day 4–10) were included.

2.2. Treatment protocol

Patients were treated in accordance with our standardized treatment protocol to avoid secondary insults, which is described in detail in previous studies [19-21]. Treatment goals were ICP ≤ 20 mmHg, CPP ≥ 60 mmHg, systolic blood pressure (sBP) > 100 mmHg, pO_2 > 12 kPa, arterial glucose 5–10 mmol/L, electrolytes within normal ranges, slight hypervolemia (3 L daily) with 0 fluid balance, and body temperature < 38 °C.

Unconscious patients were intubated and mechanically ventilated. Propofol was given for sedation and morphine for analgesia. Neurological wake-up tests were performed every day. Nimodipine was administered after arrival to the neurointensive care (NIC). The patients were treated with early aneurysm occlusion, by endovascular embolization or surgical clipping. An EVD was inserted to monitor ICP in intubated patients and cerebrospinal fluid (CSF) was drained at 15 mmHg, if ICP was high. In case of refractory intracranial hypertension, thiopental coma, and/or decompressive craniectomy were last-tier treatments. Arterial blood pressure (ABP) and CPP were maintained with intravenous fluids. Inotropes/vasopressors, at first hand dobutamine and second hand norepinephrine, were used if ABP/CPP still remained below the target thresholds.

DIND was defined as new neurological deficits and/or decreased level of consciousness when other causes, such as hydrocephalus and hematomas, were excluded. If a manifest brain infarction was excluded, hypertension, hypervolemia, and hemodilution (HHH)-therapy was initiated, including colloid fluids (albumin and dextran solutions) and moderately elevated sBP target above 140 mmHg for 5 days [22].

2.3. Data acquisition and analyses

The first radiological computed tomography (CT) scan after ictus was assessed according to the modified Fisher scale [23] by one of the authors (TSW). ICP was monitored with the EVD system (HanniSet, Xtrans, Smith Medical GmbH, Glasbrunn, Germany). ABP was monitored invasively in the radial artery at heart level. Physiological data were collected at 100 Hz, using the Odin software [24]. Pressure reactivity index (PRx) was calculated as the 5 min correlation of 10 s averages of ICP and MAP [25,26].

NT-proBNP and TnI were used as cardiac biomarkers for cardiac failure and injury, respectively, throughout the study period. NT-proBNP and TnI were measured at admission and then every morning. NT-proBNP was measured every day over the first 10 days and TnI until normalization. The testing was done at the accredited laboratory of the Department of Clinical Chemistry at Uppsala University Hospital. Normal values for NT-proBNP were below 330 ng/L and for TnI below 20 ng/L.

2.4. Outcome

Clinical outcome was assessed at around 12 months after the aSAH, by trained personnel using structured telephone interviews for the Extended Glasgow Outcome Scale (GOS-E) [27,28]. GOS-E is based on eight categories of outcome, from death (1) to upper good recovery (8). GOS-E 5–8 was considered as favorable and GOS-E 1–4 as unfavorable clinical outcome.

2.5. Statistical analysis

The analysis primarily (i) aimed to determine the association between the cardiac biomarkers (NT-pro-BNP and TnI) with ICP-/CPP-insults and cerebral pressure autoregulation and secondarily (ii) with DIND and clinical outcome.

The first 10 days post-ictus were divided into two phases – i) Early phase (day 1 to 3) and ii) Vasospasm phase (day 4 to 10). Mean values for the cardiac biomarkers and the physiological variables mentioned above were calculated for each phase. The burden of secondary insults was calculated as the percentage of monitoring time with ICP > 20 mmHg and CPP < 60 mmHg in each of the two phases. These thresholds were chosen in accordance with our management protocol [19-21]. These physiological analyses were done in the Odin software [24] and the data were then transferred to SPSS version 28 (IBM Corp, Armonk, NY, USA) for further statistical analyses.

The cardiac biomarkers and the physiological variables were compared in the early phase and the vasospasm phase with the Student's *t*-test. The association between the cardiac biomarkers with the physiological variables, the burden of secondary insults, DIND, and clinical outcome was evaluated with the Spearman rank correlation test. Multiple logistic regressions for mortality and favorable outcome, respectively, were performed with NT-proBNP and TnI in the early phase and the vasospasm phase, respectively, as independent variables in addition to age, World Federation of Neurosurgical Societies (WFNS) grade, and modified Fisher grade as baseline variables. Those with missing values were excluded from the analyses.

A *p*-value <0.05 was considered statistically significant. As this was an exploratory study, we did not adjust for multiple comparisons.

Table 1
Demography, admission status, treatments, and clinical outcome after aSAH.

Patients, n (%)	196 (100)
Age (years), mean ± SD	59 ± 12
Male/female, n (%)	69/127 (35/65%)
WFNS grade IV-V/I-III, n (%)	111/85 (57/43%)
Modified Fisher scale	
0, n (%)	0 (0)
1, n (%)	32 (16%)
2, n (%)	31 (16%)
3, n (%)	39 (20%)
4, n (%)	94 (48%)
Aneurysm location, anterior/posterior, n (%)	168/28 (86/14%)
No treatment/embolization/clip ligation/both, n (%)	1/158/35/2 (1/81/18/1%)
DIND, n (%)	47 (24%)
Thiopental (yes), n (%)	11 (6%)
DC (yes), n (%)	28 (14%)
Mortality, n (%)	16 (8%)
Favorable/unfavorable outcome, n (%)*	65/129 (34/66%)

aSAH = Aneurysmal subarachnoid hemorrhage. DC = Decompressive craniectomy. DIND = Delayed ischemic neurological deficit. IQR = Interquartile range. SD = Standard deviation. WFNS = World Federation of Neurosurgical Societies.

* 2 patients with missing outcome data.

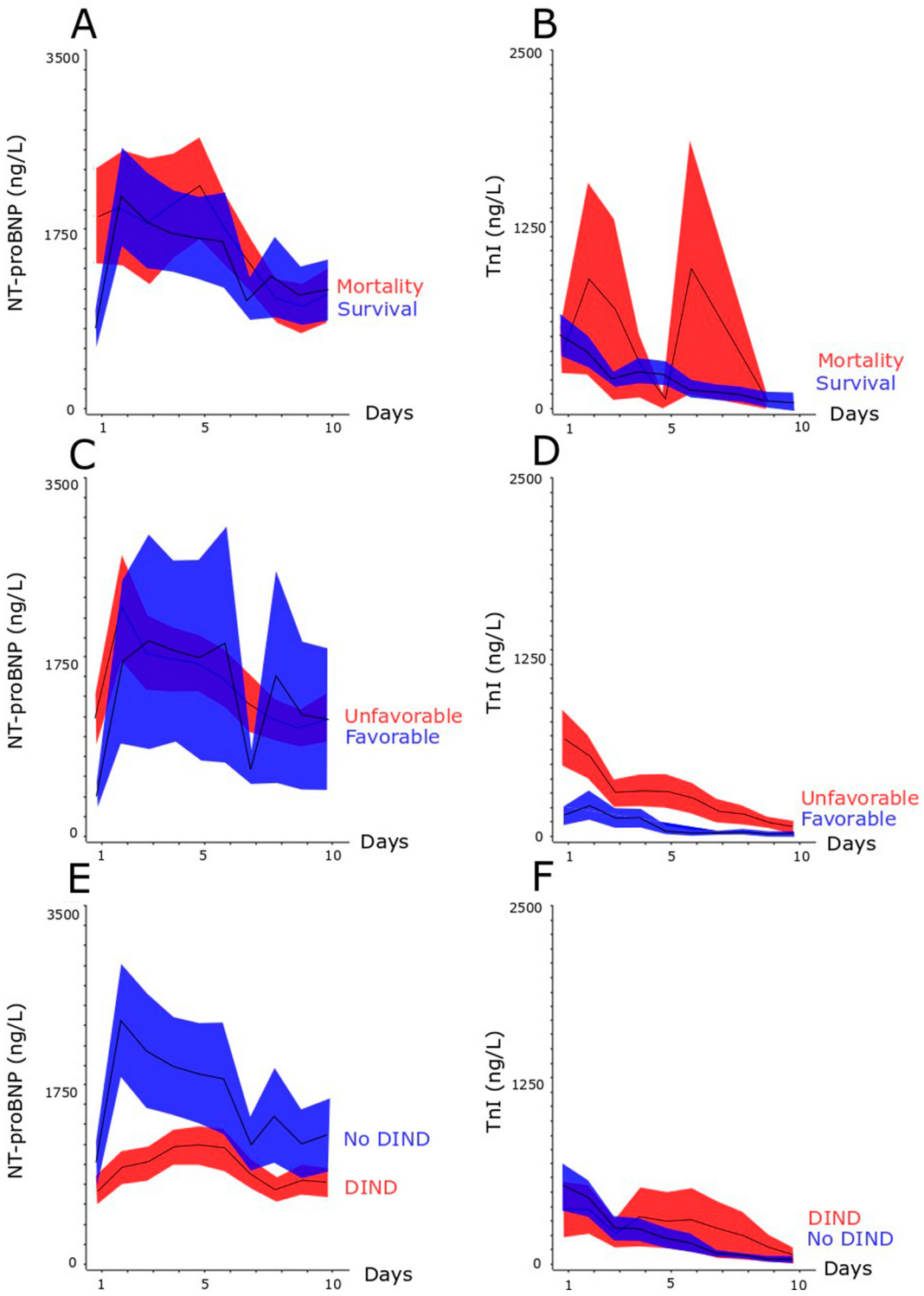

Fig. 1. A-F. NT-proBNP and TnI the first 10 days after aSAH in relation to mortality, favorable outcome, and development of delayed ischemic neurological deficits.
The figure demonstrates the daily mean values (± standard error) in the acute phase after aSAH of NT-proBNP and TnI in relation to mortality (1A-B), favorable/unfavorable outcome (1C-D), and DIND (1E-F).
aSAH = Aneurysmal subarachnoid hemorrhage. DIND = Delayed ischemic neurological deficit. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. TnI = Troponin I.

2.6. Ethics

The study was approved by the regional ethical board (2010/138 and 2010/138/1) and the Swedish Ethical Review Authority (2020–05462).

3. Results

3.1. Demography, admission variables, treatments, and clinical outcome

The clinical variables of the 196 aSAH patients are described in Table 1. Mean age was 59 (± 12) years old and 127 (65%) were female. Three (2%) patients suffered from chronic kidney failure and no patient had a diagnosis of congestive heart failure pre-ictus. The WFNS grade was IV-V in 111 (57%) of the cases. The aneurysm was located in the anterior circulation in 168 (86%) cases and the majority (81%) of the patients were treated with endovascular technique. One fourth developed DIND, 6% received thiopental, and 13% were operated with decompressive craniectomy. Four (2%) patients required dialysis due to kidney failure during NIC. Eight percent were deceased, whereas 32% had recovered favorably, after 1 year.

3.2. Temporal dynamics of NT-proBNP, TnI, and cerebral physiology in the early phase and the vasospasm phase

During the first 10 days, 175 (89%) patients exhibited at least one NT-proBNP measurement above 330 ng/l and 116 (59%) patients at least one TnI measurement above 20 ng/L. The measurement of TnI decreased as the biomarker reached normal values for the individual patients and only 66% of the patients continued with repeated measurements into the vasospasm phase. The temporal dynamics of the cardiac biomarkers are described in Fig. 1 and Table 2. The levels of both NT-proBNP and TnI peaked in the early phase and then decreased, but remained elevated above the reference values in the vasospasm phase. The systemic and cerebral physiological variables are described in Table 2. Mean heart rate, MAP, and CPP gradually increased from the early phase to the vasospasm phase, whereas mean ICP remained stable around 10 mmHg. The percentage of monitoring time with secondary insults including ICP > 20 mmHg and CPP < 60 mmHg decreased from the early phase to the vasospasm phase and were generally at or below 5% of the monitoring time.

3.3. NT-proBNP and TnI in relation to systemic and cerebral physiology in the early phase and the vasospasm phase

Higher mean values of NT-proBNP were associated with slightly lower MAP and higher burden of CPP-insults below 60 mmHg in the vasospasm phase, but not in the early phase, and did not correlate with mean heart rate, ICP, CPP, or PRx in any phase (Fig. 2 and Table 3). Furthermore, higher mean values of TnI correlated with higher heart rate and higher burden of ICP-insults above 20 mmHg and CPP-insults below 60 mmHg in the vasospasm phase, but not in the early phase, and did not correlate with mean MAP, ICP, CPP, and PRx in any phase (Fig. 3 and Table 3).

Table 2
Cardiac biomarkers and systemic and cerebral physiological variables in the early phase and the vasospasm phase after aSAH.

Variables	Early phase	Vasospasm phase	p-value
NT-proBNP (ng/L), mean ± SD	1720 ± 5180	1420 ± 4370	0.06
TnI (ng/L), mean ± SD	530 ± 1405	107 ± 346	***0.001***
Heart rate (bpm), mean ± SD	72 ± 9	79 ± 11	***0.001***
MAP (mmHg), mean ± SD	89 ± 7	95 ± 8	***0.001***
ICP (mmHg), mean ± SD	11 ± 3	11 ± 3	0.26
ICP > 20 mmHg (%), mean ± SD	4 ± 7	3 ± 6	***0.005***
CPP (mmHg), mean ± SD	77 ± 7	84 ± 8	***0.001***
CPP < 60 mmHg (%), mean ± SD	5 ± 6	2 ± 3	***0.001***
PRx (coefficient), mean ± SD	0.16 ± 0.13	0.19 ± 0.13	***0.005***

Bold and italics indicate statistical significance.
aSAH = Aneurysmal subarachnoid hemorrhage. CPP = Cerebral perfusion pressure. ICP = Intracranial pressure. MAP = Mean arterial blood pressure. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. PRx = Pressure reactivity index. TnI = Troponin I.

3.4. NT-proBNP and TnI in relation to delayed ischemic neurological deficit and clinical outcome

The biomarker for cardiac injury (TnI) was not statistically different in any phase post-ictus for those who developed DIND in comparison to those who did not (Fig. 1 and Table 3). There was a trend towards higher NT-proBNP in the no DIND-group the first days after ictus (Fig. 1). However, this did not reach statistical significance in the Spearman correlation tests (Table 3). This discrepancy was explained by that NT-proBNP varied within quite a large range, which had a greater effect on means ± standard error than the Spearman test.

Higher mean values of NT-proBNP and TnI in both phases were associated with mortality (except for TnI in the vasospasm phase) and worse clinical outcome/lower GOS-E. However, in multiple logistic regression analyses with mortality as the dependent variable and age, WFNS grade, and modified Fisher grade in addition to NT-proBNP and TnI as the independent variables, neither NT-proBNP nor TnI were independently associated with mortality (Table 4). However, younger age and lower WFNS grade were both independent predictors of lower mortality. Similar associations were found in a regression with favorable outcome as the dependent variable. Since both NT-proBNP and TnI were associated with each other, only using one of the two biomarkers at a time was evaluated in the regressions described above. However, each biomarker remained non-significant in the multiple regressions, even when evaluated separately.

4. Discussion

This study is, to our knowledge, the first to investigate the association between the cardiac biomarkers NT-proBNP and TnI in relation to high-resolution multimodality monitoring of systemic and cerebral physiology in the acute phase after aSAH. NT-proBNP and TnI were frequently elevated and associated with an increased burden of secondary ICP- and CPP-insults, but not with worse pressure autoregulation. However, the burden of the secondary insults was small (< 5%) and elevations of NT-proBNP and TnI did not translate into increased rate of DIND. Although higher values of each of the different biomarkers were associated with mortality and unfavorable outcome in univariate analyses, this did not hold true in multiple regressions. Hence, in this subset of the most severe aSAH patients who required ICP monitoring, both NT-proBNP and TnI were primarily indicators of a worse primary injury with a more complicated clinical course of secondary insults.

4.1. NT-proBNP and TnI in relation to secondary insults, cerebral pressure autoregulation, and delayed ischemic neurological deficits

NT-proBNP chiefly originates from cardiac myocytes in the left ventricle, rises in response to increased fluid load, and is used as an estimate of cardiac failure. In aSAH, higher NT-proBNP is more frequent in females with poor neurological status at admission and more extensive SAH thickness [9]. Higher NT-proBNP is associated with increased levels of catecholamines, cardiac wall motion abnormalities (WMA), lower left-ventricular ejection fraction (LVEF), and increased rate of SIC [29]. Troponin is released by cardiomyocytes in response to cardiac injury and elevations in aSAH are also related to initial injury severity and associated with WMA and SIC [5].

Several previous aSAH studies have found an association between higher NT-proBNP/BNP and increased rate of DIND and brain infarction [14,16-18,30,31], although we have previously found no such

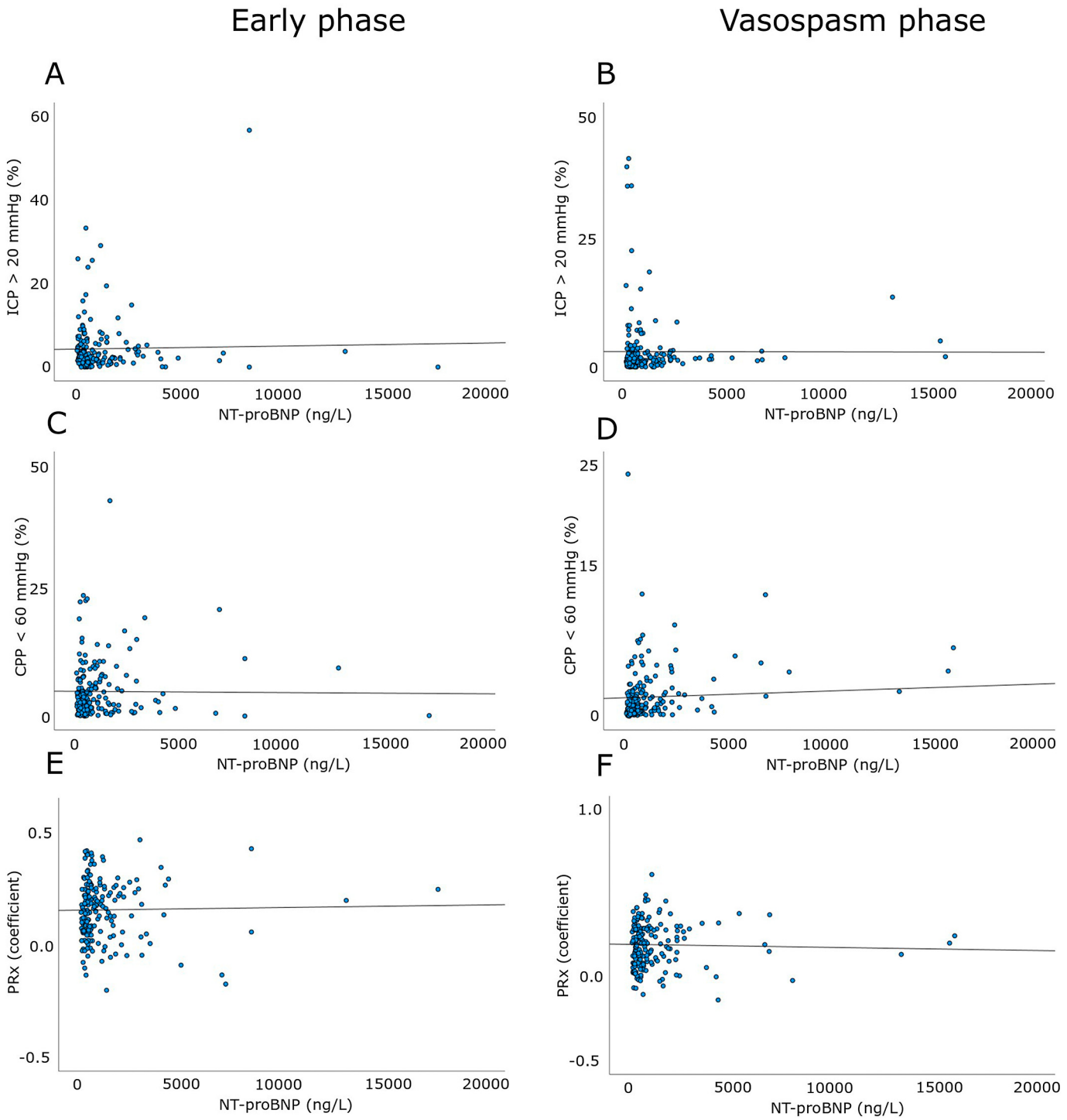

Fig. 2. A-F. NT-proBNP in relation to ICP-/CPP-insults and cerebral pressure autoregulation after aSAH in the early phase and the vasospasm phase.
The scatter plots demonstrate the association among NT-proBNP and the percentage of ICP-insults above 20 mmHg (3A-B), CPP-insults below 60 mmHg (3C-D), and with PRx (3E-F) in the early phase (day 1–3) and the vasospasm phase (day 4–10). To optimize the clarity of the plots, 3 outliers (NT-proBNP at 25000, 31000, and 56,000 ng/L) in the early phase and 1 outlier (NT-proBNP at 54000 ng/L) in the vasospasm phase were not shown. Regression lines were added to the plots.
aSAH = Aneurysmal subarachnoid hemorrhage. CPP = Cerebral perfusion pressure. ICP = Intracranial pressure. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. PRx = Pressure reactivity index.

association [9]. Similarly, but less consistently, some studies support an association between troponin and DIND/brain infarctions [12,16,30], but many studies have also found no such associations [7,10,11]. Several mechanisms have been suggested for the association between cardiac dysfunction/elevated biomarkers and DIND. First, Sviri et al. suggested a link among higher BNP, worse cerebral vasospasm severity, and higher rate of DIND [13,15]. Second, Taub et al. rather found that BNP was associated with vasospasm-independent infarction [17], possibly related to cardiac dysfunction, hemodynamic instability, and cerebral ischemia. Third, McGirt et al. found in a temporal analysis that the BNP elevation succeeded rather than preceded DIND [14], possibly as an effect of HHH-therapy or as a response to the cerebral injury development.

Table 3
Cardiac biomarkers in relation to systemic and cerebral physiology, DIND, and clinical outcome in the early phase and the vasospasm phase after aSAH – a Spearman rank correlation test.

Variables	NT-proBNP (ng/L)		TnI (ng/L)	
	Early phase	Vasospasm phase	Early phase	Vasospasm phase
Heart rate (bpm)	0.01	0.08	0.06	***0.29***[c]
MAP (mmHg)	−0.10	***−0.16***[a]	−0.04	−0.04
ICP (mmHg)	−0.07	−0.05	−0.02	0.09
ICP > 20 mmHg (%)	−0.09	0.13	−0.08	***0.21***[a]
CPP (mmHg)	−0.11	−0.13	−0.07	−0.08
CPP < 60 mmHg (%)	0.08	***0.35***[c]	0.06	***0.20***[a]
PRx (coefficient)	0.07	0.03	0.00	−0.13
DIND (yes)	0.02	0.10	−0.05	0.03
GOS-E (scale)	***−0.22***[b]	***−0.23***[c]	***−0.33***[c]	***−0.34***[c]
Mortality (yes)	***0.20***[b]	***0.20***[b]	***0.16***[a]	0.11

Bold and italics indicate statistical significance.
The table indicates the correlation coefficient between NT-proBNP/TnI and the physiological/outcome variables, based on the Spearman rank correlation test.
aSAH = Aneurysmal subarachnoid hemorrhage. CPP = Cerebral perfusion pressure. DIND = Delayed ischemic neurological deficit. GOS-E = Glasgow Outcome Scale-Extended. ICP = Intracranial pressure. MAP = Mean arterial blood pressure. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. PRx = Pressure reactivity index. TnI = Troponin I.
[a] p-value <0.05.
[b] p-value <0.01.
[c] p-value <0.001.

In comparison to previous findings, our results corroborate that elevated NT-proBNP reflects more hemodynamic disturbances including a lower MAP with a higher burden of cerebral hypoperfusion, but not worse cerebral pressure autoregulation (higher PRx). Higher TnI also correlated with more CPP-insults, but it was rather explained by more ICP-insults than a lower MAP. However, in this study, neither NT-proBNP nor TnI elevations were related to an increased rate of DIND. First, NT-proBNP, and possibly TnI, may well indicate cerebral vasospasm and autoregulatory disturbances in a broader population including more cases with low-grade aSAH. However, it is possible that this subset of mostly high-grade aSAH patients had such a severe primary brain injury leading to a severely disturbed pressure autoregulation with mean PRx around 0.2, i.e. well above 0, so that the cardiac biomarkers had little discriminative value of vasospasm/autoregulatory disturbances. Furthermore, PRx and DIND were not associated in this study (data not shown) and it is not clear if PRx actually indicates vasospasm and DIND in aSAH [21,32]. Second, despite the association between NT-proBNP/TnI and CPP insults below 60 mmHg, these insults were perhaps too infrequent in the vasospasm phase (2 ± 3%) to elicit DIND. Third, considering that the patients with DIND did not exhibit higher NT-proBNP and TnI, our results also indicate that the effect of HHH-therapy did not exert any major negative effect on serum biomarkers of cardiac failure and injury, although cardiac failure may sometimes occur without NT-proBNP elevation.

4.2. NT-proBNP and TnI in relation to clinical outcome

Previous studies indicate an association between BNP and mortality [18,33], but not with unfavorable outcome [9,16]. Similarly, and slightly more consistently, several previous studies support an association among higher troponin and mortality [11,12,16,18,30,33] and unfavorable outcome [12,16,30], although others have found no association with these outcome measures [7,10]. In this study, the univariate analyses supported that NT-proBNP and TnI elevations were associated with increased mortality and unfavorable outcome after 1 year, but not after adjustment for baseline variables including age, WFNS grade, and modified Fisher grade. Hence, the association between the cardiac biomarkers and outcome was chiefly explained by the primary brain injury [9]. However, secondary cardiac dysfunction may complicate the clinical course with e.g. more frequent secondary insults, but attentive NIC may reduce the burden of such insults which may potentially reduce eventual negative impact on the brain. The modified Fisher grade was univariately associated with lower GOS-E (data not shown), but was not an independent predictor of worse clinical outcome in the multiple logistic regressions. This was most likely a reflection of that the study population was a subset of the most severe aSAH cases who exhibited a severe hemorrhage burden (48% with grade 4).

4.3. Strengths and limitations

There were several strengths of this study. First, this was the first study combining high-resolution multimodality monitoring including ICP, CPP, and PRx in combination with the cardiac biomarkers NT-proBNP and TnI. Second, the data were analyzed in different phases, to account for different aspects of the pathophysiological course including early brain injury and vasospasm. Third, the patient population was also relatively large, which increased the reliability of the results.

There were also some limitations. First, this was a single-center study and included only the most severe aSAH cases that required ICP monitoring. This limits the external validity to some extent, both considering variations in treatment protocols including fluid balance and vasoactive agents between centers and to the sickest subset of aSAH patients. Second, only 16 patients were deceased after 1 year and the multiple logistic outcome regressions for mortality including 5 independent variables should therefore be considered very carefully. Third, the concept of DIND may be defined in many different ways and variation in definition could partly explain the conflicting results regarding the association between DIND and these cardiac biomarkers in different studies. Fourth, NT-proBNP and TnI were likely to some extent related to the use of inotropes/vasopressors, but we had not consistent data on the use of these drugs. Fifth, measurements of TnI gradually decreased as the biomarker returned to normal values. This was justified as the presence of early elevations is a good predictor of stress-induced cardiomyopathy [5], although we cannot exclude that later occult peaks in TnI did occur.

5. Conclusions

In this study cohort of aSAH patients who required ICP monitoring, higher NT-proBNP and TnI were particularly associated with an increased burden of cerebral hypoperfusion, but such insults were rare, and none of the different cardiac biomarkers were associated with worse pressure autoregulation and DIND. Although elevations in both NT-proBNP and TnI correlated with mortality and unfavorable outcome, this did not hold true after adjustment for baseline clinical variables. Hence, these biomarkers indicate a worse primary brain injury and a more complicated NIC course with a higher burden of secondary insults. Extra attentive NIC may be needed in these patients in order to attenuate any worsening regarding the cardiac injury, hemodynamic instability, and cerebral hypoperfusion.

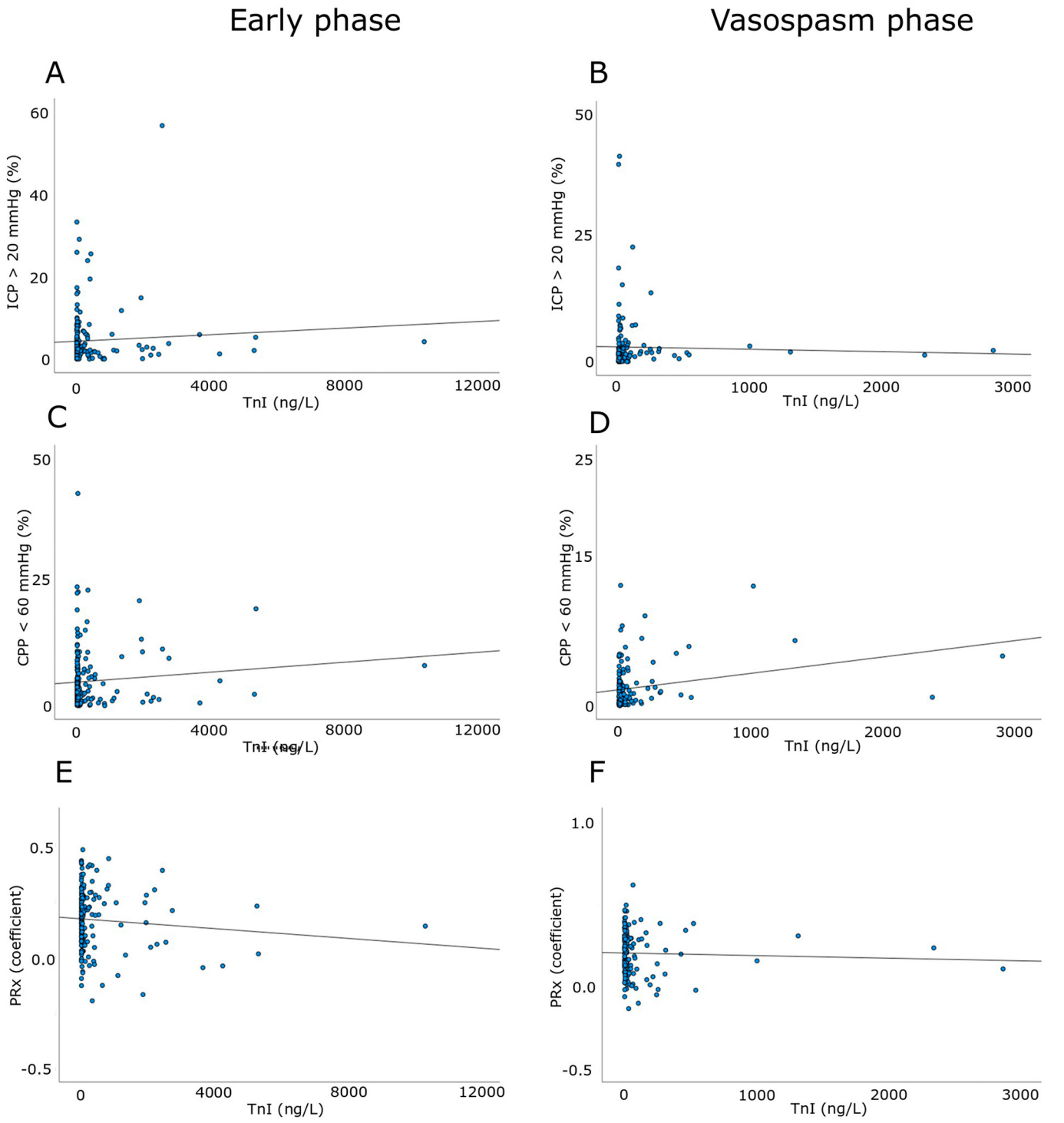

Fig. 3. A-F. TnI in relation to ICP-/CPP-insults and cerebral pressure autoregulation after aSAH in the early phase and the vasospasm phase.
The scatter plots demonstrate the association among TnI and the percentage of ICP-insults above 20 mmHg (3A-B), CPP-insults below 60 mmHg (3C-D), and with pressure autoregulation (3E-F) in the early phase (day 1–3) and the vasospasm phase (day 4–10). Regression lines were added to the plots.
aSAH = Aneurysmal subarachnoid hemorrhage. CPP = Cerebral perfusion pressure. ICP = Intracranial pressure. PRx = Pressure reactivity index. TnI = Troponin I.

Table 4
NT-proBNP and TnI in the early phase and the vasospasm phase after aSAH in relation to mortality and favorable clinical outcome– multiple logistic regression analyses.

Mortality				
Variables	Early phase		Vasospasm phase	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	***1.07 (1.02–1.13)***	***0.009***	***1.07 (1.00–1.15)***	***0.05***
WFNS (grade)	***2.16 (1.19–3.90)***	***0.01***	***4.62 (1.45–14.69)***	***0.01***
Modified Fisher scale (grade)	0.70 (0.40–1.25)	0.23	1.33 (0.53–3.32)	0.54
NT-proBNP (ng/L)	1.00 (1.00–1.00)	0.64	1.00 (1.00–1.00)	0.45
Troponin I (ng/L)	1.00 (1.00–1.00)	0.71	1.00 (1.00–1.00)	0.22
Favorable clinical outcome				
Variables	Early phase		Vasospasm phase	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	***0.93 (0.90–0.97)***	***0.001***	***0.92 (0.89–0.96)***	***0.001***
WFNS (grade)	***0.57 (0.43–0.76)***	***0.001***	***0.47 (0.33–0.68)***	***0.001***
Modified Fisher scale (grade)	0.87 (0.63–1.21)	0.41	1.03 (0.69–1.55)	0.89
NT-proBNP (ng/L)	1.00 (1.00–1.00)	0.11	1.00 (1.00–1.00)	0.08
TnI (ng/L)	1.00 (1.00–1.00)	0.33	1.00 (1.00–1.00)	0.36

Bold and italics indicate statistical significance.
Mortality, Early phase, Nagelkerke = 0.19 and Vasospasm phase, Nagelkerke = 0.33.
Favorable clinical outcome, Early phase, Nagelkerke = 0.32 and Vasospasm phase, Nagelkerke = 0.40.
aSAH = Aneurysmal subarachnoid hemorrhage. CI = Confidence interval. NA = Not applicable. NT-proBNP = N-terminal prohormone of brain natriuretic peptide. OR = Odds ratio. TnI = Troponin I. WFNS = World Federation of Neurosurgical Societies.

Funding sources

The research was supported by the Department of Neuroscience/Neurosurgery, Uppsala University, Sweden.

Disclosure

The authors declare that they have no conflict of interests.

CRediT authorship contribution statement

Teodor Svedung Wettervik: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Timothy Howells:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing. **Anders Hånell:** Conceptualization, Methodology, Writing – review & editing. **Christoffer Nyberg:** Conceptualization, Writing – review & editing. **Elisabeth Ronne-Engström:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

Acknowledgement

We express our gratitude to the personnel at the NIC Unit, Uppsala University Hospital, for meticulous patient care and gathering of outcome data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154123.

References

[1] de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365–72.
[2] Connolly Jr ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43(6):1711–37.
[3] Zetterling M, Engström BE, Hallberg L, Hillered L, Enblad P, Karlsson T, et al. Cortisol and adrenocorticotropic hormone dynamics in the acute phase of subarachnoid haemorrhage. Br J Neurosurg. 2011;25(6):684–92.
[4] Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-heart interaction: cardiac complications after stroke. Circ Res. 2017;121(4):451–68.
[5] Oras J, Grivans C, Dalla K, Omerovic E, Rydenhag B, Ricksten SE, et al. High-sensitive troponin T and N-terminal pro B-type natriuretic peptide for early detection of stress-induced cardiomyopathy in patients with subarachnoid hemorrhage. Neurocrit Care. 2015;23(2):233–42.
[6] Temes RE, Tessitore E, Schmidt JM, Naidech AM, Fernandez A, Ostapkovich ND, et al. Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrhage. Neurocrit Care. 2010;13(3):359–65.
[7] van der Bilt I, Hasan D, van den Brink R, Cramer MJ, van der Jagt M, van Kooten F, et al. Cardiac dysfunction after aneurysmal subarachnoid hemorrhage: relationship with outcome. Neurology. 2014;82(4):351–8.
[8] Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart (British Cardiac Society). 2006;92(6):843–9.
[9] Nyberg C, Karlsson T, Ronne-Engström E. Predictors of increased cumulative serum levels of the N-terminal prohormone of brain natriuretic peptide 4 days after acute spontaneous subarachnoid hemorrhage. J Neurosurg. 2014;120(3):599–604.
[10] Anetsberger A, Jungwirth B, Blobner M, Ringel F, Bernlochner I, Heim M, et al. Association of Troponin T levels and functional outcome 3 months after subarachnoid hemorrhage. Sci Rep. 2021;11(1):16154.
[11] Ramappa P, Thatai D, Coplin W, Gellman S, Carhuapoma JR, Quah R, et al. Cardiac troponin-I: a predictor of prognosis in subarachnoid hemorrhage. Neurocrit Care. 2008;8(3):398–403.
[12] Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. Circulation. 2005;112(18):2851–6.
[13] Sviri GE, Shik V, Raz B, Soustiel JF. Role of brain natriuretic peptide in cerebral vasospasm. Acta Neurochir. 2003;145(10):851–60. [discussion 60].
[14] McGirt MJ, Blessing R, Nimjee SM, Friedman AH, Alexander MJ, Laskowitz DT, et al. Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurosurgery. 2004;54(6):1369–73. [discussion 73-4].
[15] Sviri GE, Feinsod M, Soustiel JF. Brain natriuretic peptide and cerebral vasospasm in subarachnoid hemorrhage. Clinical and TCD correlations Stroke. 2000;31(1):118–22.
[16] Oras J, Grivans C, Bartley A, Rydenhag B, Ricksten SE, Seeman-Lodding H. Elevated high-sensitive troponin T on admission is an indicator of poor long-term outcome in patients with subarachnoid haemorrhage: a prospective observational study. Crit Care. 2016;20:11.
[17] Taub PR, Fields JD, Wu AH, Miss JC, Lawton MT, Smith WS, et al. Elevated BNP is associated with vasospasm-independent cerebral infarction following aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(1):13–8.
[18] Yarlagadda S, Rajendran P, Miss JC, Banki NM, Kopelnik A, Wu AH, et al. Cardiovascular predictors of in-patient mortality after subarachnoid hemorrhage. Neurocrit Care. 2006;5(2):102–7.
[19] Ryttlefors M, Howells T, Nilsson P, Ronne-Engström E, Enblad P. Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. Neurosurgery. 2007;61(4):704–14. discussion 14–5.
[20] Svedung Wettervik T, Howells T, Hånell A, Ronne-Engström E, Lewén A, Enblad P. Low intracranial pressure variability is associated with delayed cerebral ischemia and unfavorable outcome in aneurysmal subarachnoid hemorrhage. J Clin Monit Comput. 2021;36(2):569–78.

[21] Svedung Wettervik T, Howells T, Lewén A, Ronne-Engström E, Enblad P. Temporal dynamics of ICP, CPP, PRx, and CPPopt in high-grade aneurysmal subarachnoid hemorrhage and the relation to clinical outcome. Neurocrit Care. 2021;34(2):390–402.
[22] Engquist H, Rostami E, Ronne-Engström E, Nilsson P, Lewén A, Enblad P. Effect of HHH-therapy on regional CBF after severe subarachnoid hemorrhage studied by bedside xenon-enhanced CT. Neurocrit Care. 2018;28(2):143–51.
[23] Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly Jr ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21–7. discussion −7.
[24] Howells T, Elf K, Jones PA, Ronne-Engstrom E, Piper I, Nilsson P, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg. 2005;102(2):311–7.
[25] Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997;41(1):11–9.
[26] Svedung Wettervik TM, Howells T, Enblad P, Lewén A. Temporal neurophysiological dynamics in traumatic brain injury: role of pressure reactivity and optimal cerebral perfusion pressure for predicting outcome. J Neurotrauma. 2019;36(11):1818–27.
[27] Wilson JL, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow outcome scale and the extended Glasgow outcome scale: guidelines for their use. J Neurotrauma. 1998;15(8):573–85.
[28] Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow outcome scale. J Neurotrauma. 1998;15(8):587–97.
[29] Nguyen TH, Neil CJ, Sverdlov AL, Mahadavan G, Chirkov YY, Kucia AM, et al. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. Am J Cardiol. 2011;108(9):1316–21.
[30] van der Bilt IA, Hasan D, Vandertop WP, Wilde AA, Algra A, Visser FC, et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. Neurology. 2009;72(7):635–42.
[31] Kaur G, Damodara N, Feldstein E, Dominguez J, Huang KT, Ogulnick JV, et al. Relation between brain natriuretic peptide and delayed cerebral ischemia in patients with aneurysmalsubarachnoid hemorrhage. Clin Neurol Neurosurg. 2021;211:107031.
[32] Gaasch M, Schiefecker AJ, Kofler M, Beer R, Rass V, Pfausler B, et al. Cerebral autoregulation in the prediction of delayed cerebral ischemia and clinical outcome in poor-grade aneurysmal subarachnoid hemorrhage patients. Crit Care Med. 2018;46(5):774–80.
[33] Norberg E, Odenstedt-Herges H, Rydenhag B, Oras J. Impact of acute cardiac complications after subarachnoid hemorrhage on long-term mortality and cardiovascular events. Neurocrit Care. 2018;29(3):404–12.