SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical assessment of some complications of aneurysmal subarachnoid haemorrhage

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UNIVERSITY OF DEBRECEN
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Members of the Examination Committee:	Álmos Klekner, MD, PhD, DSc
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The Examination takes place at Department of Anesthesiology and Intensive Care, Library, Faculty of Medicine, University of Debrecen, 2024. November 12. 11 am.

Head of the **Defense Committee**:	Professor Norbert Németh, MD, PhD, DSc
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Members of the Defense Committee:	Álmos Klekner, MD, PhD, DSc
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The PhD Defense takes place at the Lecture Hall of Department of Emergency Care and Oxyology, Faculty of Medicine, University of Debrecen, 2024. November 12. 13 am.

1. INTRODUCTION

Subarachnoid haemorrhage (SAH) is a disease associated with high mortality and morbidity. Globally, it is responsible for approximately 9.7% of all stroke cases, which is not high in terms of rates, yet its importance stands out among brain catastrophes. Recently, the number of patients who survive stroke has increased, but in nearly 50% of survivors, quality of life does not reach pre-bleeding levels. Patients are most often of working age, with an average age of 55, and a significant percentage are unable to resume their previous work after recovery. Their functional status and cognitive function may be impaired, and depression, anxiety and post-traumatic stress are common. Adverse outcomes following a haemorrhage place a huge burden on the health service, but the impact on society, the economy and the family must also be considered. The adverse outcome is influenced by a number of factors. The most significant predictor is delayed cerebral ischaemia (DCI), which ultimately develops because cerebral perfusion is unable to meet metabolic demands. Thus, any process that reduces cerebral blood flow (CBF) or increases the metabolic demand on the brain will push the haemorrhaged patient towards the development of DCI and increase the chance of an adverse outcome. The definition of DCI has undergone a paradigm shift in recent years. For decades, the idea that DCI is caused by the development of cerebral vasospasm (CV) has held sway. The finding that areas of ischaemia do not necessarily correlate with the distribution of vasospasm and that DCI can occur without the presence of vasospasm has led to the recognition that DCI is a multifactorial process that progresses over time and culminates in the clinical manifestation of cerebral ischaemia. Although efforts to treat vasospasm have not improved the outcome of bleeding as expected, the prevention, diagnosis and therapy of vasospasm remain central to the management of patients with DCI. One of the main indications for the treatment of vasospasm is that symptomatic vasospasm is strongly associated with the development of DCI through the reduction of CBF.

To date, the only I.A. evidence-based drug for the treatment of vasospasm is the Ca^{2+} channel blocker nimodipine, which selectively acts on cerebral blood vessels. For decades, 3H therapy (hypertension, haemodilution, hypervolaemia) was considered the only treatment option. The presumed efficacy of induced hypertension is based only on uncontrolled case series. However, multicentre, retrospective data indicate that in nearly 80% of patients with symptomatic vasospasm, improvement in neurological symptoms occurred after blood pressure was raised. Taken together, these data suggest that induced hypertension still has a place in the management of vasospasm while maintaining euvolaemia. However, the question remains as to which infusion solutions can be used to maintain euvolaemia. The European Medicines Agency has recommended limiting the use of hydroxyethyl starch (HES) in critically ill septic patients, as renal failure has been reported more frequently with HES than with crystalloid solutions. However, knowing the beneficial properties of HES in microcirculation and its effect in increasing circulatory volume (CO), it remains controversial whether this recommendation also applies to SAH patients. The determinants of cerebral blood flow are CO, mean arterial pressure (MAP) and cerebral vascular resistance (CVR), but changes in CO alone can also have a significant effect on CBF. For this reason, the study of cardiovascular complications associated with SAV is important, not least of which is Takotsubo cardiomyopathy (TTS). Its importance in the context of patients treated for SAV is that it may occur in up to 1.2-26% of patients with bleeding. Left ventricular dysfunction and wall motion abnormality in TTS may pose differential diagnostic difficulties, as it is difficult to distinguish from acute myocardial infarction (AMI), and may delay definitive treatment of the aneurysm. SAV causes intracranial pressure (ICP) elevation, which may reduce CBF. This may be further aggravated by the development of vasospasm and heart failure.

The Department of Neurosurgery at the University of Debrecen is a regional centre for the treatment of SAV patients, and our Intensive Care Unit is responsible for the care of nearly 1.5 million residents. Knowing the high mortality and morbidity data of this disease, we aim to improve not only survival but also the quality of life of surviving patients by treating SAV. Early detection and treatment of the causes of DCI can contribute to improving outcomes and quality of life for survivors.

2. AIMES

2.1. To investigate prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage

In our first study we investigated the efficacy of different fluid therapies in SAH patients. Our aim was to compare the incidence of cerebral vasospasm and clinical outcome with Ringer's lactate versus HES-based prophylactic fluid replacement strategies.
In our second study, we investigated the factors influencing the development of transient heart failure, TTS and the impact of TTS on outcome in SAH patients.
Our aim was to investigate the prevalence, severity, influencing factors and impact on long-term outcome of TTS in patients treated for non-traumatic SAH.

3. Patients and methods

3.1 Investigation of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage

Between February 2014 and March 2015, our prospective, randomized, double-blind, controlled trial selected patients aged 18 years and older who were admitted to the Neurosurgical Intensive Care Unit for aneurysmal subarachnoid haemorrhage. The diagnosis of SAV was based on clinical findings and imaging studies (CT, DSA). On admission, the severity of SAV was assessed using the Hunt-Hess and Fisher scale. The treatment of the aneurysm (endovascular treatment or surgical clipping) was decided by a multidisciplinary team of neurosurgeons and neurointerventionalists. All patients were treated with 6x60 mg per os Nimodipine as primary care. MgSO4 therapy was based on laboratory results, with the aim of maintaining normomagnesaemia (target plasma concentration: 0.6-1.1 mmol/l). Exclusion criteria were if the patient or a relative did not sign a consent form or if the patient died before randomisation. Based on the patients' MAP at admission, an individual target blood pressure was set as follows: MAP at admission + 30%, not to exceed 200 mmHg

systolic. Patients received 15 mL/kg bw/day of Ringer's lactate solution intravenously as basal fluid therapy. To achieve the MAP target, they were randomized to receive infusions of 15-50 ml/kg/day of Ringer's lactate (B. Braun, Melsungen AG, Germany) or HES 130/0.4 solution (Voluven, Fresenius- Kabi, Bad Hamburg, Germany) and, if necessary, intravenous norepinephrine and/or dobutamine were added. Patients also received furosemide to maintain euvolaemia when necessary. A prophylactic fluid replacement strategy was used from day 0 to day 7. After admission to the ICU, patients were randomly allocated to 2 groups (Ringer's lactate or HES group). To ensure that an equal number of patients were allocated to each group, permuted block randomization was used. Infusions were prepared by an independent person who was not involved in the study. The neurological and TCCD examinations were performed by physicians with expertise in neurosonology, who did not know which group the patients were randomized to. This was achieved by covering the infusion label during the study. All patients were routinely monitored during ICU treatment, including continuous electrocardiogram (ECG), pulse oximetry and intra-arterial blood pressure measurement through the radial artery. Neurological status was recorded twice daily. TCCD was performed daily with a 2 MHz probe of a Siemens Acuson Antares (Siemens Healthcare GmbH, Erlangen, Germany) ultrasound machine. Vasospasm was assessed if Tamax exceeded 120 cm/s in the ACM or other segments of the circle of Willis. Severe vasospasm was considered if the Tamax was greater than 200 cm/s.

In our study, the primary endpoint was considered to be vasospasm within 14 days of admission. Secondary endpoints were mortality within 30 days, day 30 Barthel index and GOS.

3.1.1. Statistical analysis

Sample size estimates were based on previous literature data that the prevalence of vasospasm in SAV is 30%. It was assumed that the incidence of vasospasm would be reduced by 20% when using HES compared to the RL group. For α=0.05 and 1-β=0.8, 90 patients (45 patients in both groups) were required to answer our study questions. Taking potential dropouts into account, 96 patients were selected for the study, i.e. three additional patients in each group. Continuous variables with normal distribution were presented as mean and standard deviation (SD), and continuous variables with non-normal distribution were presented as median and interquartile range (IQR), and minimum and maximum values. Mean

flow rates measured in ACM were compared between the two groups by repeated measures ANOVA. For categorical variables, the $\chi 2$ test was used. A value of $p<0.05$ was considered statistically significant. Dell Statistica 13.2 (Dell Inc., Aliso Viejo, CA, USA) was used for data analysis.

3.2 Takotsubo cardiomyopathy in non-traumatic subarachnoid haemorrhage

In our prospective follow-up study, all subarachnoid haemorrhage patients over 18 years of age were included between March 2017 and December 2018, if the patient was admitted to the DEKK Neurosurgery Clinic within 48 hours of the onset of symptoms of haemorrhage. We excluded patients with trauma, angioma or arteriovenous malformation (AVM) underlying the subarachnoid haemorrhage. We also excluded bleeders with a history of known myocardial disease, including myocardial infarction, heart failure, known structural heart disease (severe, clinically significant valve regurgitation and/or stenosis), existing myocarditis, known coronary stenosis requiring balloon angioplasty, hypertrophic cardiomyopathy and pheochromocytoma. The treatment of the aneurysm (coil or clip) was based on a consultation with a neurosurgeon and a neurointerventionalist. ICU care was performed according to local protocol, which included maintenance of normovolemia, normocapnia, normoxaemia, normomagnesaemia, normoglycaemia. Nimodipine (6x60 mg) therapy and analgosedation were performed according to international guidelines. If the course of the disease required, intraventricular or lumbar drain insertion was performed. The diagnosis of TTS was based on the modified Mayo criteria. The criteria include that transient left or right ventricular wall motion abnormality usually extends beyond an epicardial coronary care area. To establish the diagnosis, we also performed laboratory tests for cardiac biomarkers (cTnI/cTnT, CK, BNP, NT-pro BNP) to demonstrate myocardial involvement. To record the ECG abnormalities most characteristic of TTS (ST depression or elevatio, negative T waves, and newly formed stem blocks), we performed 12-lead ECGs at patient admission. Based on the Mayo criteria, potential coronary artery disease excluded the diagnosis of TTS. In view of the above, we confirmed or excluded the diagnosis of TTS within the first 24 hours after admission. On admission and during the first 6 days (days 1-7), 12-lead ECGs were performed daily, cardiac biomarker levels (cTnT, CK, NT-pro BNP) were

checked. TCCD was performed at least once daily to detect the onset of vasospasm. At admission, Hunt-Hess and Fisher scores were determined and GCS and WFNS scores were recorded daily based on neurological examinations. 24-h urine collection was performed to determine urinary methanephrine and normetanephrine levels, and transthoracic echocardiography (TTE) was performed on days 1 and 7. In case of new onset of ECG abnormalities, an additional TTE study was performed.

At 30 and 180 days follow-up of the patients, the following tests were performed: 12-lead ECG, TTE, NYHA (New York Heart Association) score evaluation, and patients' outcome was graded according to GOS, Barthel and Karnofsky index scoring systems. Patients had their urine collected for 24 hours before the control study, from which a sample was taken to determine urinary methanephrine and normetanephrine levels. If TTE confirmed a wall motion abnormality, exercise ECG or exercise echocardiography, coronary CTA or conventional coronary angiography was performed as necessary. TTE scans were performed by two experienced cardiologists using a Mindray TE7 device (P4-2s 3.5 MHz harmonic imaging transducer) during hospitalization and follow-up. The investigators only knew that the patient was treated with SAH, they had no information on other ECG or laboratory parameters relevant to TTS. During echocardiography in 2D mode, parasternal short-axis and apical biventricular and tricuspid sections were used to check left ventricular systolic and end-diastolic diameters and wall motion diameter. The ejection fraction was calculated using the Simpson equation. According to the international guidelines, the diagnosis of TTS is based on hypo- or akinesis of at least one or more segments of the heart and a corresponding decrease in ejection fraction, as detected by TTE examination. The wall motion abnormality was defined using a 16-segment model and scored according to the standard method: 1-normokinesis, 2- hypokinesis, 3- akinesis, 4- dyskinesis, 5- aneurysm. To describe the number and severity of myocardial regions affected, the wall motion score index (WMSI) was calculated by dividing the sum of the wall motion score of each segment by 16. To determine the severity of TTS, EF was also taken into account and patients were divided into two groups, mild (EF>40%) and severe TTS (EF≤40%). We also assessed ejection fraction and wall motion severity during follow-up, 30 and 180 days after hospital admission. The TCCD scans were performed by 2 intensivists with expertise in neurosonology using a 2 MHz transducer on a GE Venue Go (GE Healthcare 9900 Innovation Drive Wauwatosa, WI 53226 U.S.A.) ultrasound machine. All the investigators knew was that they were examining patients being treated for SAV; no other laboratory or ECG studies were known to them. TCCD was performed through the transtemporal coronal artery in color-coded Doppler mode. After

identification of the structures of the circle of Willis, the arteries of the anterior, medial and posterior regions were examined daily on both sides. If measurements suggestive of vasospasm were recorded by TCCD scanning, ultrasound scans were continued for 21 days after the bleeding. Blood flow velocities, pulsatility index, S/D ratio measured during TCCD were recorded. Vasospasm was considered to be vasospasm if the mean flow velocity exceeded 120 cm/s, and severe vasospasm if it was above 200 cm/s. The laboratory tests were performed at the Institute of Laboratory Medicine of the Clinical Centre of the University of Debrecen. Creatine kinase activity was determined by UV kinetic method. CK-MB was determined as CK-MB activity by inhibition with antibodies against the CK-M subunit. High sensitivity Troponin T assay was performed by elechtrochemiluminescence (ECLIA) immunoassay using a Cobas e411 analyzer. An ECLIA immunoassay was also used to detect NT-pro-BNP, which has a significantly longer half-life than the active peptide and is therefore more suitable for determining the risk of TTS.
Methanephrines are usually present in the urine as glucuronate or sulphate conjugates, so acid hydrolysis was performed as a first step in the study, followed by dilution of urine samples with neutralising buffer and high performance liquid chromatography (HPLC) (ABL and E-Jasco system).

3.2.1. Statistical analysis

$\chi 2$ tests were used to compare categorical variables. For the analysis of continuous variables, the homogeneity of variances was tested using Bartlett's test and the normality of the distribution of variables was tested using Shapiro-Wilks test. For the analysis of variables with non-normal distribution and/or heterogeneous variances, non-parametric statistical tests such as the Kruskal-Wallis test were used. Binary logistic regression was used to analyse the effect of continuous independent variables (e.g. age) on binary dependent variables (e.g. prevalence of TTS). Ordinal logistic regression was used to analyse the effect of continuous independent variables on ordinal variables (e.g. severity of TTS). Generalised linear models (GLM) were used to analyse the effect of study groups and continuous independent variables on continuous dependent variables. For all statistical analyses, we used the R statistical environment version 3.6.3 (R Core Team 2020), while for the graphs we used the R package "ggplot2".

4. Results

4.1. Investigation of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage

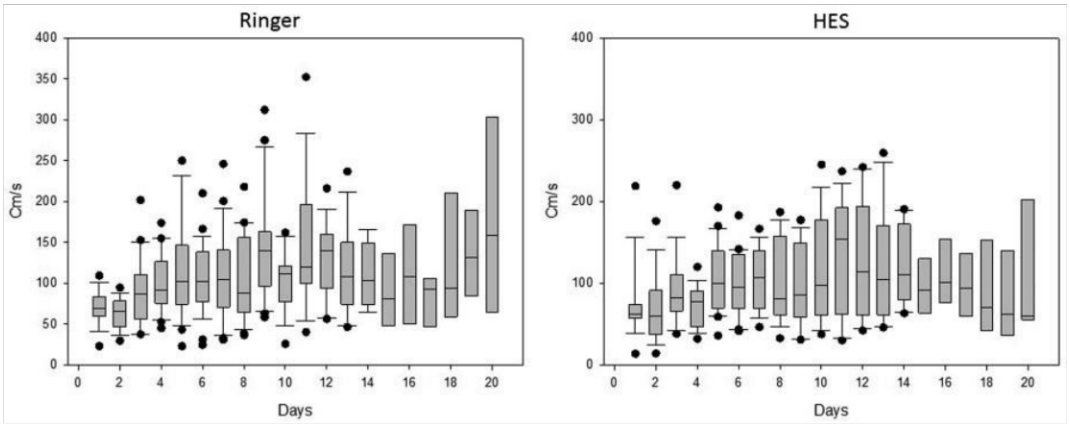
Based on our preliminary power analysis, 90 patients (45 patients per group) were required to answer our study questions. Considering potential dropouts, for safety reasons, we selected 96 patients for the study, 48 patients for the RL group and 48 patients for the HES group. In the RL group, the mean age was 49.64±11.2 years, and 15 patients were male and 33 female. In the HES group, the mean age was 51.23±10.34 years and the sex ratio was 20 male and 28 female patients. The presence of co-morbidities such as hypertension, diabetes mellitus, stroke, whether they had headache or epileptic seizure before admission was investigated. On admission to our ICU, we recorded the NIH stroke, Hunt-Hess, Fisher score, aneurysm location, whether there was cerebral oedema, cerebral infarct, intracerebral or intraventricular haemorrhage or hydrocephalus on CT scan on admission. There were no significant differences between groups in any of the baseline parameters.

4.1.1. Primary endpoint: development of vasospasm

During the study, 42 patients (43.7%) developed vasospasm, 9 of which were severe (Tamax > 200 cm/s). The distribution of vasospasm between the two groups was as follows: in the RL group, 25 out of 48 patients developed vasospasm, 6 of which were severe, whereas in the HES group, 17 out of 48 patients developed vasospasm, 3 of which were severe. ($\chi 2 = 3.41$) DSA scan did not confirm aneurysm in 22 cases, of which 9 patients were in the RL group and 13 patients in the HES group. In the patients in whom no aneurysm could be detected, moderate vasospasm developed in 2 cases (Tamax > 120 cm/s < 200 cm/s), both patients belonged to the HES group. TCCD scans were performed once a day for the first 14 days. After 2 weeks, ultrasound scans were continued if the patient had TCCD-confirmed vasospasm. In the RL group, 19 patients and in the HES group, 14 patients required

continuation of TCCD examinations between days 14 and 20. The mean flow rate measured in the ACM showed a similar pattern in both groups. There was no statistically significant difference between the treatment groups. (Figure 1.)

Figure 1.
Mean ACM blood flow velocity in the RL and HES-based groups in the "Investigation of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage" study
Median value, IQR, minimum and maximum values
RL: Ringer's lactate; HES: hydroxyethyl starch, IQR: interquartile range



4.1.2 Secondary endpoints: 30-day mortality and outcome

During the study, 4 patients died within 30 days (4.1%).
DSA failed to detect aneurysms, there were no death outcomes in either the RL or HES groups in the first 30 days. Aneurysms were confirmed in all four patients who died, 2 in the RL group and 2 in the HES group. The fluid replacement strategy did not influence the mortality outcome.
A GOS 1-3 score (death, persistent vegetative state, severe disability) indicating an unfavourable outcome was observed in 9 patients in the RL group, all 9 patients had confirmed aneurysms. Poor outcome was reported in 14 patients in the HES group, of which 13 patients had a confirmed aneurysm and 1 patient had no source of bleeding identified. In the RL group, a favourable outcome was observed in 39 patients (29 patients had aneurysms and 10 could not be detected), while in the HES group, a favourable outcome was observed in 34 patients (21 patients had aneurysms and 13 could not be detected), with a GOS of 4-5

(independent of activities of daily living). The differences seen were not statistically significant ($\chi 2$= 1,34)

The Barthel Index is a score ranging from 0 to 100, which can be used to determine the extent to which patients require assistance to carry out activities of daily living. There was no difference in the distribution of patients' Barthel scores at day 30 between the HES and RL groups. There was also no difference between the two groups when excluding patients who did not have a confirmed aneurysm and comparing only those patients who had an aneurysm. Scores between 60 and 100 on the Barthel scale indicate that patients need no or little help with their daily care. In the Ringer's lactate group, 41 patients (31 of whom were confirmed to have an aneurysm) and in the HES group, 35 patients (22 of whom had an aneurysm) were able to live independently. Moderately severe deterioration in quality of life (Barthel index 40-60) was observed in a total of 1 case, he was in the RL group and had a confirmed aneurysm. Severe disability (Barthel index <40) developed in 6 cases in the RL group, all 6 patients had DSA-detectable aneurysms. In the HES group, 13 patients developed persistent severe QoL, 1 of whom had no detectable aneurysm. (Table 1.)

To achieve the target blood pressure, 10 patients in the RL group and 9 in the HES group required norepinephrine supplementation.

Table 1.
The 30-day Barthel index in the RL and HES groups in the "Study of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage" study
Data in parentheses indicate cases where aneurysm was detected

Barthel-index	RL group (n=48)	HES group (n=48)	$\chi 2$, p
61-100	41(31)	35 (22)	$\chi 2$=4,1, n.s. ($\chi 2$= 4.31, n.s.)
41-60	1 (1)	0 (0)	
≤40	6 (6)	13 (12)	

4.2 Takotsubo cardiomyopathy in non-traumatic subarachnoid haemorrhage

A total of 136 patients met the inclusion criteria between March 2017 and December 2018. In the study group, 73 patients underwent endovascular treatment and 21 patients underwent

surgical clipping of the aneurysm. After multidisciplinary consultation with neurosurgeons and endovascular specialists, definitive treatment of the aneurysm was not performed in 42 patients. Due to hydrocephalus and ventricular hemorrhage, 40 cases required ventricular drain insertion and 5 cases required lumbar drain insertion.

4.2.1. Prevalence of TTS in the study group

Of the 136 patients, 39 (28.7%) developed Takotsubo cardiomyopathy. TTS was mild (EF>40%) in 28 (20.6%) patients and severe (EF≤40%) in 11 (8.1%) patients. The localization of the developed wall motion abnormalities was distributed as follows: classic: n = 10; midventricular: n = 1; inverse: n = 4; focal: n = 21; atypical (global): n = 3. TTS developed within 7 days of admission in 4 cases, all of which were focal in type.

4.2.2. Effect of age and sex on the incidence and severity of TTS

The incidence of TTS was not associated with the age of the patients (binary logistic regression, OR: 1.015, z = 0.821, p = 0.412). Likewise, the severity of TTS was not associated with the age of patients (ordinal logistic regression, coefficient = 0.013±S.E.0.018, OR:1.013, t = 0.729, p = 0.466).

Of the 39 cases of TTS, 30 patients were female (30/39; 77%) and 9 were male (9/39; 23%). A total of 80 female patients were selected for the study, so the 30 cases of TTS represented 37.5% of the female patients. Of the 56 male patients, the 9 TTS that developed accounted for 16% of the cases. The difference was statistically significant (Khi squared with Yates correction $\chi 2 = 6.385$, df=1, p = 0.012), i.e. TTS was more frequent in women. Wall motion disorder was more extensive in female patients. Women developed mild TTS in 23 cases (29%) and severe TTS in 7 cases (9%), while men developed mild TTS in 5 cases (9%) and severe TTS in 4 cases (7%) ($\chi 2 = 8.152$, p = 0.015), a statistically significant difference.

4.2.3. Impact of risk factors on the incidence of TTS

The incidence of TTS was not influenced by any of the risk factors we examined. Binary logistic regression calculated in a generalised linear model to examine the effect of each risk

factor on the incidence of TTS (yes/no) showed that none of the eight risk factors influenced the incidence of TTS. (Table 2.)

Table 2.
Impact of risk factors on the incidence of TTS in the "Takotsubo cardiomyopathy in non-traumatic subarachnoid haemorrhage" study

Risk factors	No TTS (n=97)	TTS (n=39)	Yates X^2
Hypertension (Yes/No)	54/43	19/20	0.297 n.s.
Arrhythmia or conduction disturbance (Yes/No)	3/94	1638	0.000 n.s.
Hypercholesterolaemia/triglyceridaemia (Yes/No)	11/86	4/35	0.000 n.s.
Diabetes mellitus (Yes/No)	4/93	1/38	0.000 n.s.
Hypothyroidism (Yes/No)	3/94	0/39	0.000 n.s.
Hyperthyroidism (Yes/No)	0/97	1/38	0.224 n.s.
Smoking (Yes/No)	47/50	19/20	0.000 n.s.
Obesity (Yes/No)	26/71	7/32	0.754 n.s.

4.2.4 Relationship between risk factors and severity of TTS

The severity of TTS was not influenced by any of the risk factors examined. Ordinal logistic regression calculated in a generalised linear model to examine the effect of each risk factor on the severity of TTS (none, mild, severe) showed that none of the eight risk factors influenced the severity of TTS.

4.2.5. Relationship between prevalence of TTS and severity scores at admission

TTS developed more frequently in patients with higher modified Fisher scores and more severe conditions. The prevalence of TTS in the different mFisher groups was as follows: 13% of patients with a score of 1, 16% with a score of 2, 30% with a score of 3 and 41% with

a score of 4 developed TTS. TTS also developed more frequently with higher WFNS scores. TTS was observed in 18% of patients with a score of 1, 39% of patients with a score of 2, 14% of patients with a score of 3, 35% of patients with a score of 4 and 48% of patients with a score of 5. The localisation of the aneurysm and haemorrhage, HH and GCS values recorded at admission did not influence the incidence of TTS.

4.2.6. Relationship between TTS severity and severity scores at admission

TTS severity was associated with the modified Fisher score, Hunt-Hess score, WFNS score and GCS. The prevalence of mild TTS was 13%, 11%, 26% and 25% in patients with modified Fisher scores 1, 2, 3 and 4, respectively, whereas severe TTS was absent in patients with Fisher score 1, increased to 5% in patients with Fisher score 2, 4% in patients with Fisher score 3 and 15% in patients with Fisher score 4. These results show that more severe bleeding is more likely to develop TTS. The HH score is used to classify the severity of bleeding according to the clinical condition of the patient. Patients with the most severe condition had the highest incidence of severe TTS. The prevalence of mild TTS (EF>40%) varied between 13% (HH score 5) and 29% (HH score 3), but no clear trend was observed. The prevalence of severe TTS increased from 0 in HH 1-2 patients to 10% in HH 3, 5% in HH 4 and 29% in HH 5. The prevalence of mild TTS varied between 14% and 28% in the five WFNS groups (score 1: 17%, score 2: 28%, score 3: 14%, score 4: 27%, score 5: 17%). The prevalence of severe TTS was absent in the WFNS groups with scores 1 and 3, severe TTS developed in 11% of patients with score 2, 8% of patients with score 4 and 30% of patients with score 5. The prevalence of severe TTS was highest among patients with the most severe GCS scores of 3-6 (30%), lower for scores 7-12 and 13-14 (8% each), and did not occur for scores 15. The prevalence of mild TTS varied between 17% and 27%, with no clear correlation between GCS scores and incidence.

When the effects of all SAV variables were examined simultaneously, we found that only the modified Fisher score influenced the occurrence of TTS, with a positive coefficient indicating that TTS was more likely to occur in patients with a higher modified Fisher score (OR: 1.719, $z = 2.923$, $p = 0.003$). Similarly, the severity of TTS was only associated with the modified Fisher score (OR: 1.764, $z = 3.071$, $p = 0.036$).

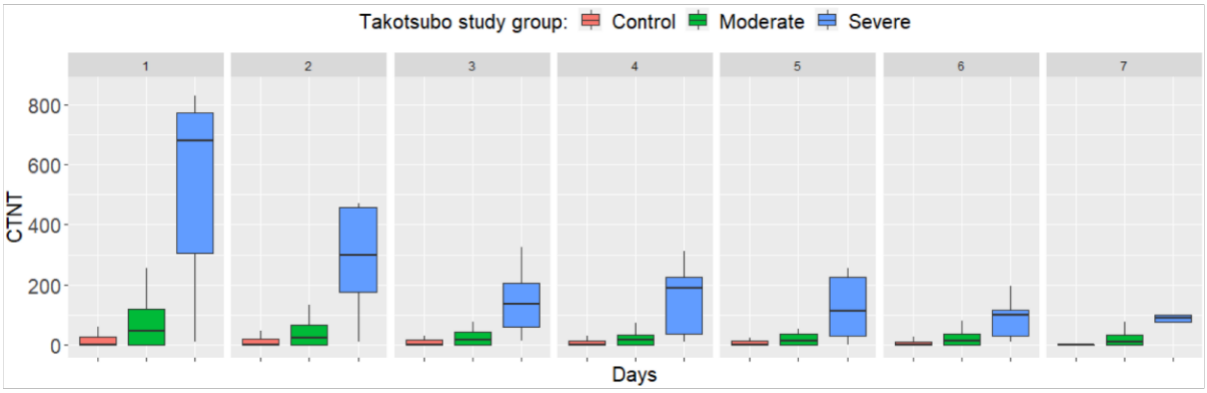
4.2.7. The relationship between the development of vasospasm and TTS

Of the patients included, 97 patients were not diagnosed with TTS, these patients constituted the control group. They developed vasospasm in 23 cases, compared to 13 out of 39 patients in the TTS group ($\chi2 = 0.74$; $p= 0.36$), indicating that TTS was not more frequent in SAV patients who developed vasospasm. In the control group, vasospasm was severe (Tamax > 200 cm/s) in 5 cases, whereas in the TTS group, vasospasm was severe in 6 cases ($\chi2 = 2.87$; $p = 0.09$).

4.2.8. Laboratory parameters

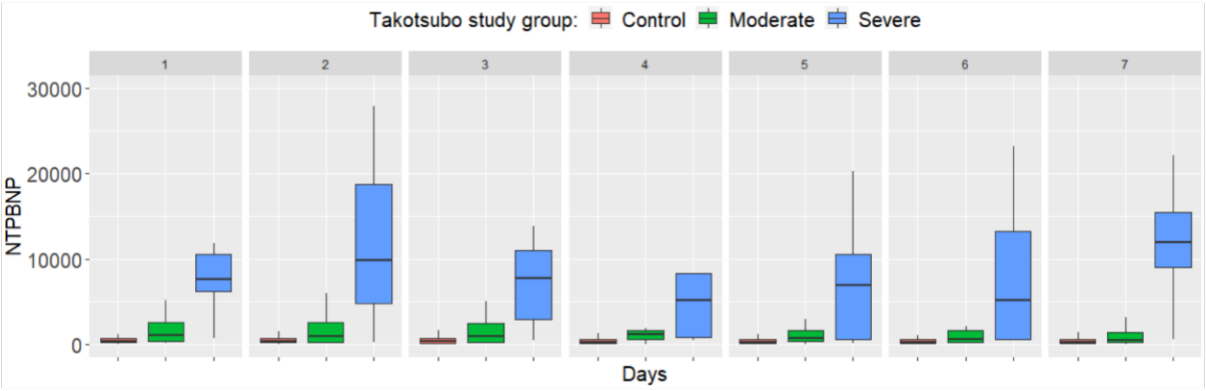
Among the measured laboratory parameters, the CK values during the first 7 days after admission were as follows between the three groups (control, mild TTS, severe TTS): in the first 7 days after admission, the CK values in the first 7 days were as follows. On day 1 ($\chi2 = 11.642$, $df = 2$, $p = 0.003$), day 2 ($\chi2 = 8.673$, $df = 2$, $p = 0.013$) and day 4 ($\chi2 = 7.478$, $df = 2$, $p = 0.024$) the differences were significant, but not on the other days. For CK-MB, the differences were significant on day 1 ($\chi2 = 9.346$, $df = 2$, $p = 0.009$), but not on the other days. For cTnT, the differences were significant on each day, mainly due to the high values measured in the severe TTS group. (Figure2)

Figure 2.
Differences in cardiac troponin T (cTnT) between study groups from day 1 to day 7. Boxplots show median value, upper and lower quartiles, and minimum and maximum values; outliers have been omitted for clarity. Differences were significant on all study days ($p<0.001$).



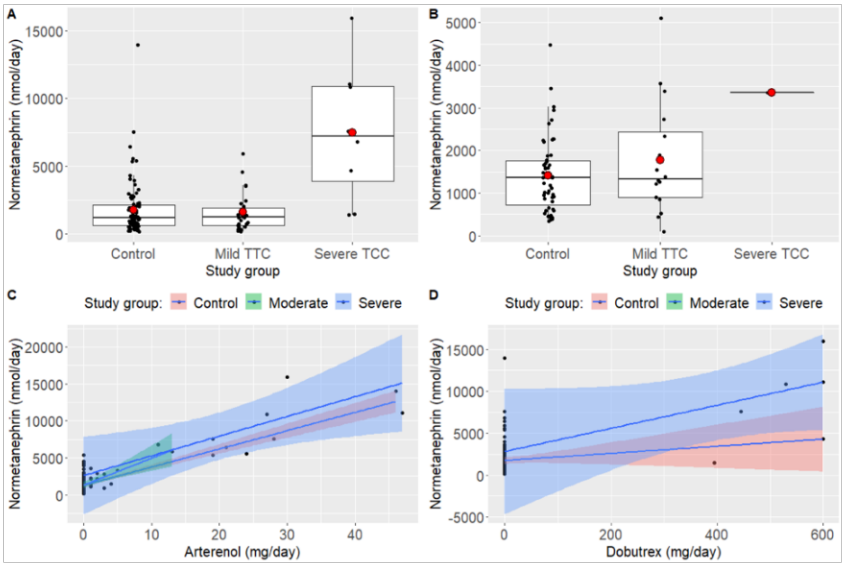
For NT-pro BNP, differences were significant on all days, due to high values in the severe TTS group. (Figure 3.)

Figure 3.
Differences in the N-terminal prohormone of B-type natriuretic peptide (NT-pro BNP) between study groups between days 1 and 7. Boxplots show median value, upper and lower quartiles, and minimum and maximum values; outliers have been omitted for clarity. Differences were significant on all study days ($p<0.001$).



Generalized linear models showed that the level of methanephrine in 24-hour urine collected did not differ between the three study groups and was not affected by the dose of norepinephrine (arterenol) or dobutamine used. This was true on the day of admission and also on days 30 and 180 of follow-up. In contrast, normetanephrine levels differed between the TTS groups. There were no significant interactions between groups and noradrenaline (arterenol) or dobutamine, indicating that the effects of the drugs were similar in each group. These results suggest that the use of noradrenaline (arterenol) and dobutamine had similar effects on urinary normetanephrine levels, so that the significant difference in urinary normetanephrine levels demonstrated did not depend on the amount of catecholamines used. The difference between study groups 30 days after bleeding was significantly different but did not reach significance, partly because of the small difference between the control and mild TTS groups and partly because of the small data in the severe TTS group. Finally, there was no difference in normetanephrine concentrations between the study groups at 180 days after bleeding (generalized linear model, $F2.54 = 0.209$, $p = 0.812$). (Figure 4.)

Figure 4.
Urinary normetanephrine levels on the day of admission (A) and 30 days later (B), and the effect of noradrenaline (arterenol) (C) and dobutamine (dobutrex) (D) on normetanephrine concentrations on the day of admission. Boxplots show data points, median value, upper and lower quartiles, and minimum and maximum values; red dots indicate means. Shaded areas in plots C and D indicate 95% confidence intervals.

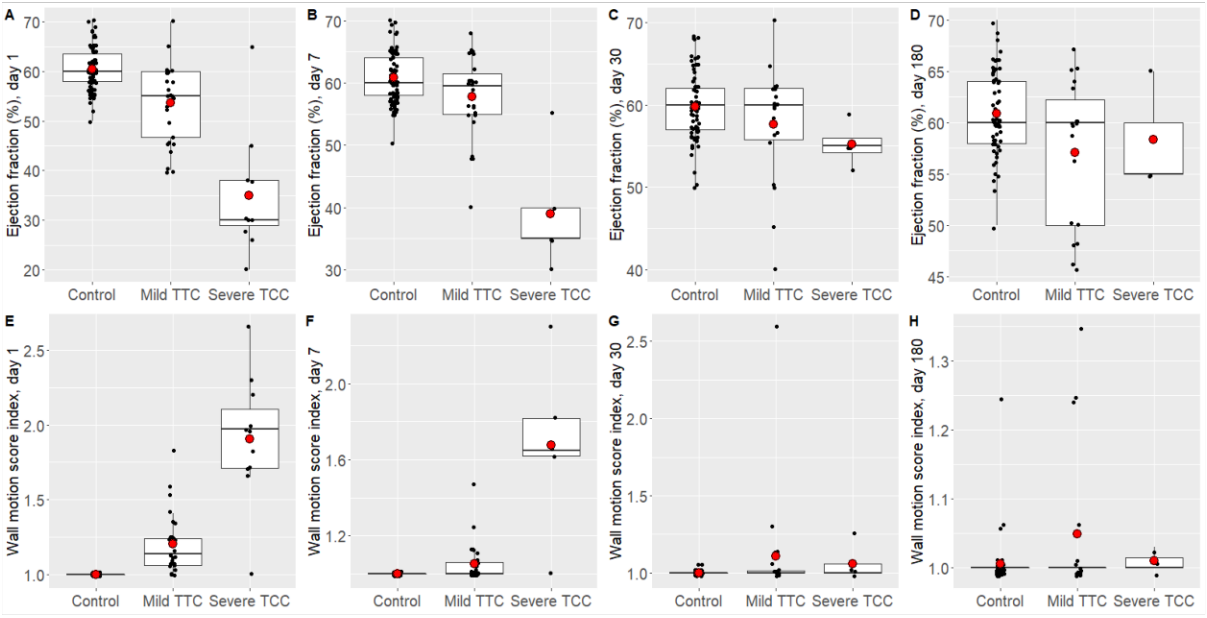


4.2.9 Temporal variation of parameters measured by echocardiography

The ejection fraction was significantly lower in severe TTS patients than in the non-TTS control group, and intermediate but closer to the level of controls in mild TTS patients, both on day 1 and day 7. These differences were significant at day 30, but did not reach significance level and no difference could be detected at day 180. In TTS patients, the ejection fraction improved gradually during the follow-up period, but no complete improvement was observed, with contractility still impaired at day 180.

The WMS index for wall motion was highest in patients in the severe TTS group and low in the mild TTS and control groups. The differences were significant on all study days and the difference was still detectable after 180 days. (Figure 5.)

Figure 5.
Differences of ejection fraction (%) (A-D) and wall movement score index (E-H) in the study groups on days 1, 7, 30 and 180. Boxplots show data points, median value, upper and lower quartiles, and minimum and maximum values; red dots indicate means.



4.2.10. Relationship between severity of TTS and mortality

At the end of the 180-day follow-up period, 70 (74.5%) of 84 patients in the control group, 22 (81.5%) of 27 patients in the mild TTS group and three (27%) of 11 patients in the severe TTS group had survived. The difference in mortality rate was significant ($\chi 2 = 12.395$, df = 2, $p = 0.002$). The number of patients who died at different stages of follow-up was as follows:

- Days 1-7: no TTS group: n = 9; mild TTS: n = 2, severe TTS: n = 6
- Days 8-30: no TTS: n = 6; mild TTS: n = 3; severe TTS: n = 1
- Days 31-180: no TTS: n = 9; mild TTS: n = 0; severe TTS: n = 1

4.2.11. Relationship between the severity of TTS and patient outcomes

GOS, Barthel and Karnofsky scores were higher in patients in the control (non-TTS) and mild TTS groups than in the severe TTS group. All differences were significant except for the difference in Barthel scores during the second control, indicating that severe TTS is associated with worse long-term clinical outcome in patients.

5. Discussion

5.1. Investigation of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage

In our study "Investigation of prophylactic fluid replacement strategies in aneurysmal subarachnoid haemorrhage", we compared the efficacy of two fluid therapies in patients treated for SAH. The fluid therapy was adjusted to provide the patient with a personalised target blood pressure value. We examined the difference in efficacy between the two fluid therapies, crystalloid Ringer's lactate and colloid HES 130/0.4 solution. We investigated the effect of fluid therapies on whether either fluid therapy is more effective in preventing the development of vasospasm. We also investigated whether the 30-day short-term outcome differed between the two groups. We found no difference in any of the study endpoints (incidence of vasospasm, 30-day outcome). To the best of our knowledge, this is the first prospective, randomized, double-blind study comparing the prophylactic efficacy of Ringer's lactate and HES 130/0.4 in SAH patients. The European Medicines Agency has recommended limiting the use of HES in critically ill septic patients, as they are more likely to develop renal failure than crystalloid solutions. However, it remains controversial whether this recommendation also applies to patients with aneurysmal SAH. Ibrahim and Macdonald performed a post-hoc analysis of the CONSCIOUS-1 trial and compared the outcome of colloid- and crystalloid-based groups in patients with aneurysmal SAV. This trial focused on the efficacy of clazosentan and left the fluid strategy to the choice of the treating physician. There was no difference between colloid and non-colloid groups in terms of DCI incidence, GOS and Rankin scores. A similar result was found by Lennihan and colleagues, who administered 5% albumin as colloid therapy and found that prophylactic hypervolaemic fluid therapy did not increase CBF compared with euvolaemic therapy. Their results suggested that hypervolaemic fluid therapy is not beneficial in preventing DCI. Egge et al. also found no advantage of hypervolaemic, hypertensive, haemodilutional therapy (using albumin and reomacrodex) compared with normovolaemic strategies in terms of the incidence of vasospasm and clinical outcome. In a retrospective analysis of HES- and crystalloid-based prophylactic fluid replacement strategies, no differences were found between the two groups in terms of in-hospital mortality and GOS. The incidence of vasospasm was higher and ICU stays longer in the HES group compared with the crystalloid-based group. It is difficult to

compare our results with these previous studies because they used a different concept and a different type of colloid. In our study, the colloid we used was Voluven, which is a III generation HES (tetrastarch) formulation. It does not accumulate in the plasma, is stored in the tissues to a lesser extent than second-generation products and is cleared from the body within 24 hours. It can increase intravascular volume by 100% of the volume of Voluven infused due to its molecular structure. This effect is sustained for 4 hours and an increase in CO and CBF can be achieved with a lower volume load. In our study, the use of colloids for prophylactic purposes was based on the idea that they improve cardiac performance due to their beneficial haemorheological effects, thus leading to CBF improvement, thus reducing the likelihood of vasospasm. Subsequent studies have shown that hypervolaemia can be as detrimental to SAH patients as hypovolaemia and that positive fluid balance is associated with worse outcomes. In line with this, recent recommendations suggest that fluid therapy should aim to maintain euvolaemia and avoid prophylactic hypervolaemia. In line with the weak recommendation of the consensus document by Diringer et al, we have shown in the present randomized trial that the use of colloids in euvolaemic prophylactic therapy does not provide an advantage over crystalloid therapy in terms of vasospasm incidence and clinical outcome. In our study, the rate of cerebral vasospasm was 30% lower in the HES group than in the RL group, but we could not demonstrate a beneficial effect on outcome. A large clinical trial could provide a definitive answer, but such a trial is not warranted as there is no evidence to suggest a benefit of HES. In addition, the European Medicines Agency's Safety Committee has recommended that marketing authorisations for HES solutions be suspended throughout the European Union because of the higher incidence of renal failure in critically ill septic patients compared with crystalloid solutions. Our study had some limitations. Firstly, our fluid replacement strategy was based on invasive blood pressure measurements and daily fluid balance data, we did not use other invasive haemodynamic monitoring. This may have resulted in imbalances in fluid status at certain times of the day, but we maintained euvolemia in all patients based on fluid balance data. Second, a prophylactic fluid replacement strategy was followed for the first 7 days after admission. This may seem a short time for prophylaxis, but the decision was made to cover the most likely period of vasospasm onset. Also, a limitation of our study is that the determination of vasospasm was based on transcranial color-coded Doppler measurements. CT, DSA cannot be used as a screening test because of the increased radiation exposure, so we performed them only in cases where blood flow velocities were increased and the neurological status of the patients deteriorated despite the elevation of blood pressure.

5.2 Takotsubo cardiomyopathy in non-traumatic subarachnoid haemorrhage

Our study is one of the first prospective studies to evaluate the incidence, predisposing factors and long-term clinical outcome of TTS following aneurysmal subarachnoid haemorrhage in a parallel, complex manner. Our results contribute to a better understanding of the natural history of TTS following SAH. In our study, we searched for associations between pathophysiological factors, clinical presentation of TTS and outcome parameters. Since all SAV patients were consecutively included, the incidence reported in our study group reflects the true incidence of TTS. An important novelty is the systematic, prospective, long-term (180 days) follow-up of echocardiographic parameters in parallel with cardiac biomarkers and concomitantly collected urinary catecholamine concentrations. Based on EF, the TTS group was divided into two groups. Based on a predefined ejection fraction threshold of 40%, we distinguished between mild and severe forms of TTS in the acute phase of subarachnoid hemorrhage. This grouping of EF showed good correlation with long-term outcome of patients. Our study was the first to show that in severe TTS cases, cardiac wall motion abnormalities can persist up to 6 months after the onset of SAH. Our study demonstrated that cardiac wall motion abnormality was detectable in 28.7% of cases. Severe TTS had higher mortality and worse long-term outcomes. The prevalence of TTS based on previous literature ranged from 1.2% to 26%. The differences can be explained, at least in part, by the evolution of the definition of TTS over time. In Talahma's study, the typical classic form of TTS was found in 2.2% of SAH patients, while others reported rates of 8.8%, 11%, 22% and 27%. The prevalence may have been influenced by the nature of the study (prospective or retrospective) and the timing and frequency of echocardiographic studies. The prevalence of TTS in SAH may be underestimated in the majority of studies and prospective studies with systematic echocardiographic follow-up are encouraged. In the present study, we included only patients who were admitted within 48 hours of bleeding and underwent TTE within 24 hours of admission. ECGs were obtained daily and cardiac biomarkers were monitored. In addition to the tests scheduled for days 1 and 7, if significant ECG changes were found, echocardiography was performed immediately. We therefore believe that the 28.7% prevalence of TTS in our study group reflects the true incidence of this condition. n the offline analysis, a mild and a severe group of TTS patients were arbitrarily defined. The predefined threshold of ejection fraction of 40% was established based on clinical experience and literature data, Based on this grouping, the prevalence of severe TTS was found to be 8.1% in

SAV, which is in line with previously published prevalence rates. Our study confirmed that TTS develops more frequently in women than in men. This finding is in line with data from previous studies. TTS occurred in 77% of women and we found more severe cases in women. In two retrospective studies, the proportion of women was 100% and 78%, respectively. In a prospective study by Kothavale and colleagues, the proportion of women was 68%. The differences may be explained by the fact that estrogen deficiency in postmenopausal women results in increased sympathetic effects and endothelial dysfunctiosis, which makes the cardiac microcirculation more vulnerable during severe disease. In contrast to previous findings, we found no association between the prevalence of TTS and cardiovascular risk factors and comorbidities. This is explained by the relatively high prevalence of cardiovascular risk factors in the Hungarian population. We found that the prevalence of TTS and the severity of TTS are associated with the severity of bleeding, as measured by modified Fisher, HH, WFNS and GCS scores This indicates that the more severe the SAV at admission, the more severe the TTS during the course of the disease. Similar observations have been published by Talahma and colleagues. Malik and colleagues also found a positive correlation between bleeding severity, clinical status of patients (higher Hunt-Hess score) and left ventricular ejection fraction. Kothavalet and colleagues and Kilbourn and colleagues found that severe neurological symptoms (HH 3-5) have predictive value for predicting regional wall motion abnormalities. It should be noted that in our present study, binary regression tests showed that of the condition severity scores, only the modified Fisher score at admission was significantly associated with TTS severity. Follow-up analyses of cardiac biomarkers showed that both cTnT and NT-pro BNP values increased from the day of admission in both the mild and severe TTS groups. In the mild group, the levels of cTnT and NT-pro BNP normalized from day 3, while in the severe group, higher levels of these biomarkers persisted until day 7. The temporal pattern of elevation of cardiac troponin is consistent with previous observations confirming that troponin can detect left ventricular dysfunctiot in SAH with high sensitivity and elevated serum BNP was significantly associated with regional wall motion abnormality. It is widely accepted that catecholamines play a key role in the development of TTS. Elevated plasma catecholamine (adrenaline and noradrenaline) concentrations are a common finding in TTS patients. At rest, the source of noradrenaline acting on cardiac receptors is the adrenal medulla, with 2-8% of the rest released from sympathetic nerve endings. In the acute phase of TTS, increased concentrations of circulating catecholamines have been observed at the myocardial level. Furthermore, the density of β2 receptors is higher in the apical than in the basal part of the ventricle, whereas β1-adrenergic receptors are predominantly expressed at

the base. The physiological increase in adrenaline levels results in a switch of the β2-adrenergic receptor from Gs to Gi to prevent the proapoptotic effect of intense β1- adrenergic receptor stimulation. This switching leads to a negative inotropic effect in the apical part of the left ventricle, and the increased sympathetic activity may cause endothelial dysfunctiosis and consequent microvascular stenosis of the coronary arteries, which may contribute to myocardial ischemia. Consistent with these findings, in our present study we found that urinary methanephrine concentrations did not differ between TTS and non-TTS patients, whereas normetanephrine was elevated in TTS patients at admission. This difference was no longer observed during follow-up at days 30 and 180. Normetanephrine concentrations were not affected by dobutamine or norepinephrine treatment. Consistent with these observations, Akashi and colleagues also demonstrated an improvement in cardiac sympathetic hyperactivity in TTS patients using myocardial scintigraphy. It is hypothesized that severe TTS itself may contribute to the increase in normetanephrine production and exacerbation of TTS through systemic effects of myocardial dysfunction as part of a vicious cycle, but our data are insufficient to confirm this. By definition, the wall motion abnormalities in TTS patients are transient and improve with time along with the ejection fraction of the heart. Kim and colleagues showed that ejection fraction improved from 38% to 61% on average over 6 weeks of follow-up. In a study by Templin and colleagues, 86.5% of patients with TTS were found to have a reduced left ventricular ejection fraction (mean 40.7), which recovered over time at 60-day follow-up. Similarly, Dias reported an improvement in left ventricular ejection fraction, from an initial mean of 32.1% to 54% at 6 months follow-up. In our study, EF in mild cases normalised by day 7, while in the severe TTS group, the reduced EF persisted for the first 7 days. Although no statistically significant difference was detected between the TTS and non-TTS groups at 30 days, it should be noted that EF was still lower in the severe cases and that the difference was not statistically significant may be explained by the relatively small sample size. Importantly, the WMSI differences persisted after 180 days in the severe TTS group, indicating that cardiac contractility had not fully recovered after 6 months, despite the normalization of global left ventricular ejection fraction. In our study group, the severity of TTS significantly affected patient outcome and mortality during 180 days of follow-up. Mortality at 6 months was significantly higher among patients with severe TTS, whereas mortality in patients with mild TTS was similar compared with SAV patients who did not develop TTS. The mortality rate measured in the present study (33.3%) was lower than that in Kilbourn's study (47%), but slightly higher than that found by Talahma (28%) and Abd (26%). For those who were alive at day 180, both GOS scores and Karnofsky scores were

significantly lower in the severe TTS group than in the mild TTS group. The Barthel index in the severe TTS group reflected worse disease outcome only at day 30 in the present study. There are few studies that have examined the long-term outcome of TTS in SAH. Similar to our results, Crago and colleagues showed a difference in the Barthel index at 30 days after SAV, but not at day 60. Mutoh et al. reported worse 3-month functional outcome in TTS patients with <40% EF using the modified Rankin scale. We should mention some limitations of our study. This was a single-centre follow-up study with a 22-month inclusion period and, consequently, the number of patients included was limited. The follow-up of vasospasm with TCCD is also a limitation of the study. Vasospasm can be accurately diagnosed by angiography, however, the scan is invasive and has a significant radiation burden, therefore we decided to perform TCCD scans daily to monitor blood flow velocity. If clinical and/or ultrasound signs of vasospasm were found, cerebral angiography was performed. We did not measure serum levels of adrenaline and noradrenaline because we believe that sampling blood for these parameters would represent a rapidly changing snapshot, whereas methanephrine and normetanephrine levels measured from a sample of urine collected over 24 hours may be more representative of tissue exposure to these hormones. Finally, in the analysis of the results, we arbitrarily defined mild and severe forms of TTS based on the ejection fraction, based on the fact that previous studies have shown that the critical ejection fraction threshold for cardiovascular complications and long-term outcome is between 40-45%.

6. New findings

- We found no difference in the incidence of vasospasm within 14 days of admission between crystalloid and HES-based prophylactic euvolaemic fluid strategies in patients with aneurysmal SAH.
- We found that there was no difference between crystalloid and HES-based prophylactic euvolaemic effusion strategies with respect to secondary endpoints (mortality within 30 days, Barthel index and GOS).
- The results of the present study do not support the use of HES as a prophylactic treatment strategy for SAH patients.
- We found that TTS develops in 28.7% of patients with aneurysmal subarachnoid haemorrhage and severe TTS occurs in 8% of SAH cases.

- We confirmed that the incidence of TTS is associated with the severity of bleeding, as characterised by modified Fisher and WFNS scores at admission.
- We conclude that the severity of TTS may be an independent predictor of mortality and outcome in the 6 months after disease onset.
- We conclude that systematic and regular follow-up of ECG and echocardiographic abnormalities is warranted for early detection of TTS in patients with subarachnoid haemorrhage.

7. Summary

The most significant predictor of adverse outcome in SAH is delayed cerebral ischaemia (DCI), which develops because cerebral perfusion is unable to meet metabolic demands. Heart failure due to both symptomatic vasospasm and Takotsubo cardiomyopathy (TTS) can impair cerebral blood flow (CBF), increasing the risk of DCI.
In our first study, we investigated the prevalence of vasospasm following SAV and the outcome using the Barthel index and GOS under RL and HES 130/0.4-based fluid replacement strategies. We did not detect differences in any of the study endpoints (incidence of vasospasm, 30-day outcome). To the best of our knowledge, this is the first prospective, randomized, double-blind study comparing the prophylactic efficacy of Ringer's lactate and HES 130/0.4 in SAH patients.
In our second study, we investigated the prevalence, predisposing factors and long-term clinical outcome of TTS in patients treated for non-traumatic SAH. Our study is one of the first prospective studies to assess the association between aneurysmal subarachnoid hemorrhage and TTS in a parallel and complex manner.
Since all SAV patients were consecutively included, the 28.7% incidence reported in our study group reflects the true incidence of TTS. The incidence of TTS is associated with the severity of bleeding, as characterized by modified Fisher and WFNS scores at admission. More severe SAV developed TTS more frequently.
Our study does not support the use of HES as a prophylactic management strategy for SAH patients. TTS severity may be an independent predictor of mortality and outcome in the 6 months after disease onset. Systematic and regular follow-up of ECG and echocardiographic abnormalities is warranted for early detection of TTS in SAH patients.

8. Publication list

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Registry number: DEENK/44/2024.PL
Subject: PhD Publication List

Candidate: Judit Gál
Doctoral School: Doctoral School of Neurosciences
MTMT ID: 10037411

List of publications related to the dissertation

1. Molnár, C., **Gál, J.**, Szántó, D., Fülöp, L., Szegedi, A., Siró, P., Nagy, E. V., Lengyel, S., Kappelmayer, J., Fülesdi, B.: Takotsubo cardiomyopathy in patients suffering from acute non-traumatic subarachnoid hemorrhage: A single center follow-up study.
   PLoS One. 17 (5), 1-20, 2022.
   DOI: https://doi.org/10.1371/journal.pone.0268525
   IF: 3.7

2. **Gál, J.**, Fülesdi, B., Varga, D., Fodor, B., Varga, E., Siró, P., Bereczki, D., Szabó, S., Molnár, C.: Assessment of two prophylactic fluid strategies in aneurysmal subarachnoid hemorrhage: a randomized trial.
   J. Int. Med. Res. 48 (7), 1-10, 2020.
   DOI: http://dx.doi.org/10.1177/0300060520927526
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List of other publications

3. Szántó, D., Luterán, P., **Gál, J.**, Nagy, E. V., Fülesdi, B., Molnár, C.: Diagnosis and Management of Takotsubo Syndrome in Acute Aneurysmal Subarachnoid Hemorrhage: a Comprehensive Review.
   Rev. Cardiovasc. Med. 24 (6), 177-189, 2023.
   DOI: http://dx.doi.org/10.31083/j.rcm2406177
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4. Szántó, D., **Gál, J.**, Tankó, B., Siró, P., Jakab, Z., Luterán, P., Fülesdi, B., Molnár, C.: Pediatric Neuroanesthesia: a Review of the Recent Literature.
   Curr. Anesthesiol Rep. 12, 467-475, 2022.
   DOI: http://dx.doi.org/10.1007/s40140-022-00540-2
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   DOI: http://dx.doi.org/10.1186/s12871-016-0284-0
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6. Molnár, C., Simon, É., Kazup, Á., **Gál, J.**, Molnár, L., Novák, L., Bereczki, D., Sessler, D. I., Fülesdi, B.: A single preoperative dose of diclofenac reduces the intensity of acute postcraniotomy headache and decreases analgesic requirements over five postoperative days in adults: A single center, randomized, blinded trial.
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   In: Neuroanesztézia és neurointenzív ellátás. Szerk.: Fülesdi Béla, Tassonyi Edömér, Molnár Csilla, Medicina Könyvkiadó Zrt., Budapest, 39-44, 2014.

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DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

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