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Troponin and non-traumatic subarachnoid haemorrhage. Results from a study of 243 consecutive patients

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aneurysmal subarachnoid haemorrhage, non-aneurysmal, non-traumatic subarachnoid haemorrhage, cardiac troponin, cardiac markers, neurogenic cardiac dysfunction, stress cardiomyopathy

ABSTRACT

Introduction: Subarachnoid haemorrhage (SAH) is a devastating event, with a mortality of up to 50%. Acute cardiac dysfunction is common after such an event, and it is known to have a negative impact on the outcome of these patients. Cardiac troponin release occurs frequently after SAH and represents an early biomarker for neurogenic cardiac dysfunction.

Objective: The present study aimed to evaluate the impact of a raised troponin value on the outcome of SAH patients.

Methods: This is a prospective observational study held between 2014-2017 at the University Emergency Hospital, Bucharest. Data on clinical admission status, high-sensitivity troponin I, ECG and echocardiographic evaluation results, ICU length of stay and in-hospital mortality rate. Statistical analysis was performed using non-parametrical Mann-Whitney and chi-square tests. The results were considered significant at $p<0.05$.

Results: A total of 335 consecutive patients with non-traumatic SAH were admitted during the study period. 92 of them were excluded and 243 were analyzed, 203 with aneurysmal SAH and 40 with non-aneurysmal, non-traumatic SAH. High-sensitivity troponin I reached its peak level 48 to 72 hours after SAH and was higher in patients with aneurysmal SAH. For all SAH patients, its median and peak values on days 1 and 2 were correlated with the ICU length of stay and inversely correlated with in-hospital length of stay. For the first 3 days, the median and maximum troponin values are higher in patients who died compared with those who survived and were discharged home (p-value < 0.001). Predictors of an elevated troponin on day 1 are loss of consciousness at ictus, a high Hunt and Hess and Fisher Scale grade, intraventricular haemorrhage and cerebral midline shift.

Conclusions: The release of cardiac troponin is a valuable marker of neurogenic cardiac dysfunction in the first 3 days after SAH. The study replicates other data in the literature and highlights the association between SAH severity, early troponin elevation and in-hospital death.

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Introduction

Subarachnoid hemorrhage (SAH) is a medical emergency, still associated with a high morbidity and mortality, despite the recent advancement in its treatment. The fact that it affects people in the prime of their lives makes it an important public health concern. It is a well-known fact that subarachnoid hemorrhage is associated with neurogenic myocardial dysfunction, of which cardiac troponin is a reliable marker. Up to 63% of aneurysmal SAH patients have a cardiopulmonary involvement and 23% of them die as a result of such a complication (1-3). The cardiac dysfunction becomes a sign of the severity of SAH, as well as a marker of bad outcome. It is associated with neurologic complications, such as vasospasm and delayed cerebral ischemia, and with a high in-hospital mortality (4-6). The diagnosis of such a myocardial dysfunction is made taking into consideration the early electrocardiographic changes, the release of cardiac troponin and NTproBNP and the echocardiographic wall motion anomalies.

Moreover, this stress cardiomyopathy is encountered early in the clinical evolution of aneurysmal SAH, as the majority of patients who are diagnosed with such a complication have a lower arterial blood pressure and thus a higher need for vasopressors, more ST-T anomalies and even a high value of the cardiac troponin at the moment of their hospital admission (7). Troponin has a high sensibility for detecting the cardiopulmonary stress encountered in SAH, with up to 70% of patients having a rising troponin value in the first two days from the aneurysmal rupture. Furthermore, a high troponin value is corelated with a prolonged corrected QT interval on the electrocardiography and echocardiographic anomallies (3)(4)(7-12).

Materials and method

We conducted a prospective observational study. All consecutive adult patients admitted to the Neurosurgical or the Intensive Care Unit of the University Emergency Hospital, Bucharest, between December 2014 and December 2017 were included. Their identity was anonymized and all of them were treated by their attending doctors according to national and international protocols for SAH, without any interference from the lead author of this paper, who collected the data. A series of data were collected, among them preexisting pathologies and known SAH risk factors, clinical status on admission (neurological and cardiovascular parameters, such as Glasgow Coma Scale grade, arterial pressure and heart rate) vasopressor requirement, oxygenation index, SAH extension on CT (Fisher Scale grade, intracerebral and intraventricular hemorrhage extension), ECG and echocardiographic evaluation results, high-sensitivity troponin I value, ICU length of stay and in-hospital mortality. Exclusion criteria were represented by: traumatic SAH, preexisting cardiac disease (ischemic heart disease, congestive heart failure, cardiac pacing, atrial fibrillation or atrial flutter), chronic renal failure, fluid balance and electrolytic anomalies or treatment with drugs that might affect the ECG or a period longer than 24 hours between the debut of symptoms and the transfer to the University Emergency Hospital. Statistical analysis was performed using SPSS v27.01.0 (SPSS Inc., Chicago, Ill., USA). Data was represented using means or medians and non-parametric Mann-Whitney tests were performed to analyze the difference between groups. Categorical data was assessed using chi-square tests. A p value <0.05 was considered statistically significant.

Results

Between December 2014 and December 2017, there were 335 adult patients with SAH admitted to the University Emergency Hospital in Bucharest. We excluded 92 of them due to criteria mentioned above, so 243 of them were studied – 203 with aneurysmal SAH and 40 with non-aneurysmal, non-traumatic SAH.

Aneurysmal SAH

Of the 203 patients with aneurysmal SAH, the majority were women (55.17%) and lived in an urban area (61.58%). The mean age was 51.4±12.1 years old, with the youngest patient being 20, and the oldest 79 years old. The mean age was 52 years old for women and 49 years old for men. The mean body mass index was 28 (interquartile range IQR 26, 31), 102 patients (50,2%) were smokers and 42 (20.7%) were using alcohol. 45 patients (22%) were dyslipidemic, 48 (23.6%) were hypertensive, 11 (5.4%) had a history of stroke and 20 patients (9.9%) had diabetes. The mean duration from symptom debut to hospital admission was 2.67 hours for people coming from rural areas, and 1.64 hours for people coming from urban areas. The median for the

admission Glasgow Coma Scale score was 7.5 (IQR 5, 14). Most of the patients with a ruptured aneurysm (135 or 66.5%) were admitted to the Intensive Care Unit, with a median ICU stay of 1 day (IQR 0, 4) and a median hospital stay of 9 days (IQR 1, 19). More than half of them (113 or 55.7%) died during their hospital stay.

Table 1. Data for day 1

Parameter	All patients (n=243)	Non-aneurysmal SAH (n=40)	Aneurysmal SAH patients (n=203)
Median for systolic arterial pressure (IQR)	135 (125,155)	140 (135,150)	135 (125,155)
Median for mean arterial pressure (IQR)	101.67 (88.34,11)	105.83 (94.6,113)	101.67 (85,115)
No. and percentage of patients with vasopressor treatment	42 (17.3%)	1 (2.5%)	41 (20.2%)
Median for heart rate (IQR)	85 (70, 95)	80 (71.25, 90)	85 (70, 95)
Median for oxygenation index (IQR)	300 (263.5, 327)	371.5 (321.5, 448.5)	290 (260, 321.75)
Mechanically ventilated	145 (59.7%)	20 (50%)	125 (61.6%)
Median for troponin level (IQR)	0. 62 (0.02,1.24)	0.36 (0.17,0.59)	0.63 (0.09,1.24)
No. and percentage of patients with high troponin value	113 (74.8%)	6 / 9 (66.7%[1])	107 / 142 (75.4%[1])
Median for corrected QT interval (IQR)	410 (378, 448)	386 (372, 418)	416 (380, 452)
No. and percentage of patients with prolonged corrected QT interval	47 (19.3%)	0	47 (23.2%)

[1] Percentage based on total number of patients with available troponin value for day 1

Other data collected for day 1 are shown in table 1. The median for the maximum high-sensitivity cardiac troponin I level was 1.02 ng/ml, with an interquartile range of 0.26 to 1.96 ng/ml. For those patients in whom high-sensitivity cardiac troponin I level was measured, its value increased from day 1, reaching a peak value on day 3 (48 to 72 hours from the rupture of the aneurysm). Table 2 shows data regarding the high-sensitivity cardiac troponin I values for patients with aneurysmal SAH.

Table 2. High-sensitivity cardiac troponin I level

	Day 1	Day2	Day 3
Median for troponin level (IQR)	0.63 ng/ml (0.09,1.24)	0.98 ng/ml (0.29,1.91)	1.7 ng/ml (0.85,2.63)
No. and percentage of patients with high troponin value	107 / 142 patients (75.4%[1])	67 / 84 patients (79.8%[1])	41 / 41 patients (100%[1])

[1] Percentage of the patients with available troponin value for day

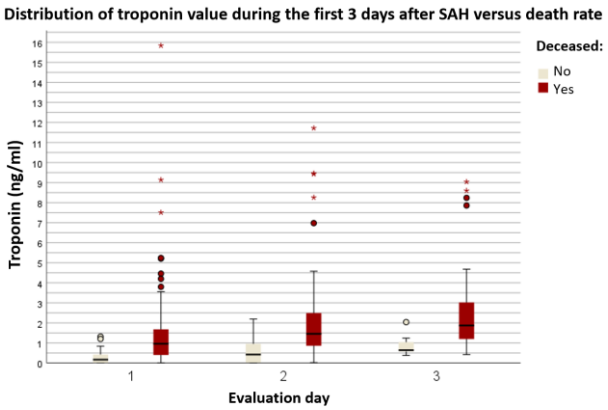

Figure 1. Distribution of troponin value during the first 3 days after SAH versus death rate

For all patients (aneurysmal and non-aneurysmal, non-traumatic SAH), both maximum troponin value ($p<0.001$) and troponin value from day 1 ($p<0.028$) and day 2 ($p<0.001$) were correlated with their ICU stay, and inversely correlated with their in-hospital stay ($p<0.001$ for all). Moreover, for patients with aneurysmal SAH, these values were correlated with

their in-hospital stay (p<0.001) and not with their ICU stay. Furthermore, the maximum troponin value and the troponin level during the first 3 days were significantly higher in patients who died during their hospital stay compared with those who were discharged (p<0.001 for all) (Figure 1).

Table 3. Predictors of elevated troponin (troponin >0.03 ng/dL) on day 1

Variable	No of patients with elevated troponin on day 1 N=107 (%)	OR (95%CI)	P value
Loss of consciousness at ictus	68 (63.6%)	5.03 (2.14, 11.83)	<0.001
Hunt&Hess grade IV or V	86 (80.4%)	4.86 (2.14, 11.02)	<0.001
Fisher Scale grade III or IV	84 (80%)	10 (4.16, 24)	<0.001
Intraventricular hemorrhage	51 (47.7%)	5.46 (1.97, 15.15)	<0.001
Midline shift	51 (47.7%)	4.4 (1.69, 11.46)	0.001

Admission clinical and radiographic variables (CT) predictive of increased day 1 high-sensitivity cardiac troponin I levels included: loss of consciousness at ictus, higher Hunt and Hess grade (IV and V), higher Fisher scale grade (III and IV), intraventricular hemorrhage and midline shift on admission CT.

Non-aneurysmal, non-traumatic SAH

This group consists of 40 patients, with 57.5% originating from urban areas and 42.5% of them being women. The mean age was also 51.48±11.87 years old, with the youngest being 28, and the oldest 71 years old, in both men and women. The mean body mass index was also 28 (IQR 26, 31), 15 patients (37.5%) were smokers and 6 (15%) were using alcohol. 14 patients (35%) were dyslipidemic, 9 (22.5%) were hypertensive, and 13 patients (32.5%) had diabetes. None had a history of stroke. The mean duration from symptom debut to hospital admission was 4.4 hours for both rural and urban areas, but with a median value of 2 hours for people coming from rural areas, compared with 5 hours for people coming from urban areas. The median for the admission Glasgow Coma Scale score was 11.5 (IQR 5.25,15). Just like patients with aneurysmal SAH, more than half of the people in this subgroup were admitted to the Intensive Care Unit (21 or 52.5%), with a median ICU stay of 1 day (IQR 0, 4) and a median hospital stay of 18.5 days (IQR 5.25, 26).Less than half of them (17 or 42.7%) died during their hospital stay.

Discussion and conclusions

Our data correlate well with those found in the literature when it comes to the general characteristics of the people in the 2 subgroups: women are more affected by SAH caused by aneurysm rupture, while more men are affected by non-aneurysmal, non-traumatic SAH. Both subgroups are represented by people in their prime (about 51 years old), coming from urban areas (13)(14). As expected, smoking was the most prevalent risk factor encountered in our cohort, in half of the patients. A series of studies cites smoking as the most important modifiable risk factor for aneurysmal rupture (15-20). The fact that alcohol consumption was declared by only about a quarter of the patients may be so because of the social stigma associated with it, or because of the underreporting bias – people tend to underestimate their alcohol intake. A high alcohol consumption represents an important risk factor for aneurysm rupture (15)(17)(21)(22). In contrast to the literature (15)(17)(21-23), not finding hypertension as a main risk factor for SAH may be explained by the general lack of preventive medicine in our country, with a certain number of people believing that you should visit a doctor only when you are “sick”, without realizing that a lot of diseases are, in fact, “silent killers”.

It was important to study all of these risk factors, as all of them are also risk factors for cardiac disease, where troponin plays a key role. On the one hand, for aneurysmal SAH, the more rapid hospital admission for people coming from urban areas compared to those from rural areas could be easily explained by their proximity to a hospital. On the other hand, vice-versa was observed for non-aneurysmal, non-traumatic SAH. This seems to represent a paradox – lighter symptoms compared to those produced by the rupture of an aneurysm make people living in an urban area ignore them for a longer period of time, precisely because they can access medical support at any time they feel they finally need to. Nevertheless, the time frame between symptom debut to hospital

admission remains short in terms of troponin release and detection. This is important as it did not interfere with the trend of our troponin results.

A lower median value of the Glasgow Coma Scale Score, a higher percentage of ICU admission and a higher death rate for patients with aneurysmal SAH versus non-aneurysmal, non-traumatic SAH was observed, as expected, due to its more severe evolution, with a known high mortality (1)(24)(25). The cardiac dysfunction in patients with SAH was readily apparent when analyzing general data, like mean arterial pressure, need of vasopressors, heart rate, and even oxygenation index and need of mechanical ventilation, or specific parameters like, troponin level and corrected QT interval on the electrocardiogram. The subgroup of aneurysmal SAH patients had a lower mean arterial pressure and a higher need of vasopressor treatment, a lower oxygenation index and a higher percentage of mechanically ventilated people, all of which are markers of a cardiac involvement. Moreover, a higher percentage of aneurysmal SAH patients had an abnormal troponin level, with a median troponin value almost double the one observed in non-aneurysmal, non-traumatic SAH. The fact that troponin elevation is detected early in the evolution of SAH is very useful in order to detect the incidence of cardiac dysfunction immediately after SAH.

For the first day of hospital admission, our study revealed a high frequency of high-sensitivity cardiac troponin I elevation - 74.8% out of the 151 patients who were tested in the entire SAH group, with a higher percentage in the aneurysmal SAH subgroup (75.4% out of the 142 patients who were tested) compared to the non-aneurysmal, non-traumatic subgroup (66.7% out of the 9 patients who were tested). We may have overestimated the true incidence of an elevated troponin I value, due to the fact that not all patients included in the study were tested. On the one hand, other studies (8)(26-28) revealed that only 20% to 40% of the patients with aneurysmal SAH had a detectable troponin I release. On the other hand, all these other cited studies used cardiac troponin I assays, whereas we investigated the dynamics of high-sensitivity cardiac troponin I, which, as its name suggests, has much lower limits of detection (29). Therefore, new studies may be needed in order to describe de dynamics of high-sensitivity cardiac troponin I assays in patients with SAH. Troponin reaching a peak on day 3, that is 48 to 72 hours after aneurysmal rupture in our study, is also well correlated with other literature references (30).

We found that high-sensitivity cardiac troponin I measurements after SAH have prognostic significance. A raised value on day 1 and 2 (which represent the first 48 hours after SAH) is significantly correlated with the ICU stay, and inversely correlated with in-hospital stay. This suggests a more severe clinical evolution for patients with a high troponin value and supports the idea that cardiac dysfunction associated with SAH may be involved in their poor outcome. Moreover, the fact that maximum troponin level, as well as troponin values during the first 3 days after SAH are significantly higher in patients who died, versus patients who were discharged home suggests that cardiac troponin should be routinely measured in SAH patients, in order to be able to offer a more intensive management for these patients. Furthermore, these results reinforce the general recommendation of a thorough cardiac monitoring, including serial troponin measurements, especially during the first 3 days in all SAH patients.

Patients with more severe SAH grades should be primarily monitored closely for cardiac dysfunction, as they demonstrated to be more likely to develop an elevated level of serum cardiac troponin I. There was a strong correlation between the extent of cardiac troponin I elevation and various parameters of SAH severity, such as loss of consciousness at ictus, a high Hunt and Hess grade, intraventricular hemorrhage, midline shift and a high Fisher scale grade. These results demonstrate the neurogenic origin of heart injury in aneurysmal SAH patients. Further research is needed to investigate whether certain measures to optimize cardiac treatment after SAH improve outcome.

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