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CARDIAC DYSFUNCTION OF PATIENTS WITH NONTRAUMATIC SUBARACHNOID HEMORRHAGE: MONITORING, PROGNOSTIC FACTORS

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Introduction

Subarachnoid hemorrhage (SAH) represents a medical-neurosurgical emergency, with an uncertain prognosis; it can induce severe disability or even death, despite early diagnosis and treatment.

The effects of SAH are both neurological, produced by the arterial blood jet causing a mechanical and toxic injury to the adjacent brain tissue, accompanied by transient global cerebral ischemia, as well as systemic, with multiple organ failure, such as cardiac and pulmonary.

Neurogenic cardiac dysfunction, frequently encountered in SAH and correlated with an uncertain functional prognosis, underlines the need to define prognostic serum markers (to identify patients at risk of neurological complications, before their clinical deterioration), to improve the management of these patients, as well as to evaluate the economic burden of these neuro-cardiac complications, which involves: management in multidisciplinary centers, with high-performance investigations, long hospitalization, including stays in ICU departments, and advanced, complex therapeutic support.

The present thesis aims to contribute to the already existing literature, through a multidisciplinary approach, which combines notions of neurosurgery, cardiology, and intensive care, of a complex public health problem, thus meeting the need for continuous improvement of the diagnosis and management of the neurogenic stunned myocardium in patients with intracranial pathology, such as non-traumatic SAH.

The study carried out as part of this doctoral thesis, at the Bucharest University Emergency Hospital, for the monitoring and prognosis of neurogenic cardiac dysfunction produced by non-traumatic SAH, is a current topic of particular interest, being the first at the national level.

I. Current state of knowledge

1. General information about nontraumatic SAH

Spontaneous SAH is produced by aneurysmal rupture in 85% of cases, and two-thirds to half of the remaining cases are attributed to non-aneurysmal perimesencephalic SAH, a benign form of SAH. [1-4] The remainder, approximately 5% of spontaneous SAH cases, have various rare causes. [1][2][5]

At the moment, there is no up-to-date epidemiological data on the incidence and prevalence of SAH in Romania.

The degree of neurological damage and the extent of hemorrhage at admission are the most important predictors of prognosis and possible neurological complications. SAH scoring is constructed based of the previously mentioned elements, using, most frequently, 3 scales: Hunt and Hess, Fisher and the classification of the World Federation of Neurosurgical Societies. [5-7]

The therapeutic measures initially consist of the stabilization of vital functions: ensuring the airways (for the comatose patient), ventilation (for those hypoxemic or those who hypoventilate), cardiocirculatory support (either for those hypotensive, which would aggravate cerebral suffering, or for those with severe hypertension, who are at the risk of rebleeding), as well as the suppression of possible convulsive seizures. Afterwards, the patient is evaluated clinically together with cerebral CT imaging and urgently transferred to a center with expertise in the treatment of this pathology, with multidisciplinary teams and with a high turnover of patients. Aneurysm treatment can be done by: surgical clipping or endovascular coiling (preferred), as soon as possible, during the first 72 hours, to avoid vasospasm; by BP control, until securing the ruptured aneurysm and thus balancing the risk of ischemia, rebleeding and maintaining cerebral perfusion pressure; the BP value that reduces the risk of bleeding has not been precisely established, but a decrease in systolic BP below 160 mmHg is reasonable; by intravascular volume control (euvolemia to prevent late cerebral ischemia); by management of cardiopulmonary complications; by seizure management (possible anticonvulsant prophylaxis in the immediate posthemorrhagic period, but no long-term anticonvulsants); by fever treatment (in the acute phase, aggressive fever control until normothermia is achieved); by careful control of blood sugar (avoidance of hypoglycemia); by deep vein thrombosis prophylaxis; by management of late cerebral ischemia (PO nimodipine to all patients with SAH, maintenance of euvolemia, no prophylactic hypervolemia or balloon angioplasty before the onset of angiographically

detected vasospasm, transcranial doppler to monitor vasospasm, CT or MR angiography of the brain (TOF sequence) identifies regions of possible ischemia cerebral, induces hypertension, unless BP is elevated basally or if cardiac status contraindicates; by correction of anemia (by erythrocyte mass transfusion, especially in those at risk of late cerebral ischemia; optimal target Hb is unknown); by hyponatremia (prevented and corrected with fludrocortisone and hypertonic saline solutions). [6-11]

Short-term prognosis is directly correlated with neurologic status on admission, inversely correlated with patient age, with the amount and extent of bleeding on initial CT. In the long term, compared with the general population, patients with aneurysmal SAH have higher mortality and are at higher risk of nonfatal vascular events such as MI or stroke. For patients with non-aneurysmal SAH, the prognosis is generally better, although the final outcome depends on the comorbidities of each patient, as well as the type of non-aneurysmal SAH, this pathology having as its etiology a heterogeneous group of conditions. The better prognosis is in patients with perimesencephalic SAH, who generally do not have significant neurologic deficits and life expectancy is not shortened compared to the general population. [12-16]

2. Cardiac dysfunction associated with intracranial pathology

2.1. Pathophysiology of cardiac dysfunction associated with intracranial pathology

The brain-heart axis is activated by direct stimulation of certain brain areas, which leads to a sympathetic or parasympathetic ANS response, or by a neuroendocrine response associated with a clinical picture of "sympathetic storm". [17-19] The neurocardiac axis is made up of a complex group of neural pathways and interactions: the prefrontal cortex, the insular cortex, the anterior cingulate gyrus, the amygdala (paleocortex), and the brainstem. [19-23] This brain-heart interaction, and especially the dire consequences on the heart when it is affected, has been described after any type of major brain injury. Damage to the insular cortex and subcortical regions induces an imbalance of the ANS, with increased sympathetic tone and massive release of catecholamines within minutes. The release of catecholamines appears to occur locally, intramyocardially, from sympathetic nerve endings, followed by increased intracellular calcium concentration and mitochondrial dysfunction. [17][18][20][24-29]

2.2. Cardiac manifestations in patients with nontraumatic SAH

Aneurysmal SAH is both a neurological disease and a pathology with an important systemic impact, with an increased incidence of cardiopulmonary complications (between 39% and 63%; frequently described in patients without preexisting known cardiac disease and without electrolyte disturbances; contributes to a bad prognostic, 23% of deaths are due to cardio-pulmonary complications). This cardiovascular dysfunction is more likely as the deficit neurological is higher, being a marker of SAH severity. Its presence is associated with a poor prognosis, late cerebral ischemia, as well as high mortality, and the diagnosis is established with the help of ECG changes, cardiac markers with increased values (especially Tn and NT-proBNP), as well as through the presence of disorders of kinetics highlighted by echocardiography. [24][27][30-34]

2.2.1. Echocardiographic changes

Currently, an incidence between 50% - 100% of cardiac manifestations is described, the most common being ST segment abnormalities (15-51%) or T wave, typically symmetrical, negative T wave (12-92%), as well as prolongation of the QTc interval (45-71%). ECG changes appear within the first 48 hours after the neurological injury, but the

duration of their persistence is variable, usually disappearing 6 weeks after the event. However, these changes are nonspecific, tend to be asymptomatic, variable in evolution, and disappear with the resolution of the neuronal injury. [17][20][22][29][30][31][33][34]

2.2.2. Changes in the level of cardiac markers

2.2.2.1. Troponin

20% to 70% of patients with SAH experience an increase in serum levels of TnI, which reaches a peak value in the first 2 days after the onset of hemorrhage, with a gradual decrease in the following days. The increase in TnI is correlated with the presence of echocardiographic changes – with an LVEF < 50% and/or kinetic abnormalities, as well as with prolongation of the QTc interval. [20][24][29][33][34][37-41] At present, the positive predictive value of elevated TnI levels at the onset of aneurysmal SAH is not yet well established, although this appears to be associated with the risk of vasospasm, late cerebral ischemia, poor neurologic outcome, and increased mortality. [20][30][39][42-44]

2.2.2.2. NT-proBNP

An increased level of BNP and NT-proBNP is found in more severe aneurysmal SAH, which is associated with diastolic or systolic cardiac dysfunction, global or regional, with increased TnI levels, as well as with cerebral vasospasm, cerebral infarction, late cerebral ischemia, early mortality and neurological outcome in aneurysmal SAH. The BNP value rises rapidly after the onset of the neurological injury, with a peak on days 2-4, correlates positively with the TnI values in the first days, and returns to the basal value after 1-2 weeks. The plasma level of BNP is higher in comatose patients than in conscious patients with SAH and in the case of ruptured cerebral aneurysms at the AcoA level. [20][24][30][31][37][41] [45-54]

2.2.2.3. Echocardiographic changes

70% of patients with aneurysmal SAH have LV diastolic dysfunction, whereas in 10% to 41% of cases of aneurysmal SAH, echocardiography reveals regional kinetic disturbances, which typically do not affect the cardiac apex and do not respect a vascular distribution territory - stunned myocardium of neurogenic cause, which represents the most severe form of cardiac damage among patients with SAH. [33][43][45][55][56] There are also cases of global impairment of left ventricular systolic function, as well as the apical ballooning, typical of Takotsubo cardiomyopathy. This systolic myocardial dysfunction occurs early, within the first 2 days, is reversible (an improvement in LVEF is observed 3-42 days after

the injury), and appears to be more common in females, smokers, the elderly, and patients with a greater Hunt and Hess score, which supports the hypothesis of a neurally mediated process. [20][22][24][30][33][34][38][42][46][57-62] The fact that the peak level of TnI does not correlate with the degree of LV dysfunction (estimated by LVEF), together with the reversible character of this dysfunction, suggests that these cardiac complications are not based on myocardial necrosis. [24][29][30][31][33][34][39][48][58][63]

II. Personal contributions

3. Working hypothesis and general objectives

The present study had as its working hypothesis the existence of cardiac dysfunction of neurogenic origin in patients with non-traumatic SAH (aneurysmal and non-aneurysmal), proposing to demonstrate the existence of prognostic factors for the occurrence of this cardiac dysfunction among patients diagnosed with spontaneous SAH, as well as the role of that the development of such cardiac injury of neurogenic cause has in the development of neurological complications as well as in the survival of these patients.

The scientific objectives proposed for the solution were: establishing risk factors for the cardiac dysfunction of the patient with non-traumatic SAH, specifying the prognostic relevance of the electrocardiographic changes, the increased enzyme level of highly sensitive cardiac troponin I, the increased serum level of NT-proBNP and the left ventricular dysfunction, all observed echocardiographically in the cardiac dysfunction of the patient with non-traumatic SAH and creating a protocol for monitoring cardiac dysfunction in patients with non-traumatic SAH.

4. General research methodology

It was a national, unicentric, observational, retrospective study, carried out on patients over 18 years of age, admitted consecutively to the Neurosurgery or ICU departments of The University Emergency Hospital of Bucharest, between December 2014 and December 2017, with the diagnosis of SAH, established by imaging . The agreement of the department heads, as well as that of the Hospital Ethics Commission were obtained. Patient data were anonymized.

Inclusion criteria: age over 18 years, non-traumatic etiology of SAH, to have performed on admission a native brain CT for diagnosis, a standard set of analyzes (to include ionogram, urea, creatinine) and at least one ECG trace.

Exclusion criteria: traumatic etiology of SAH, history of ischemic heart disease (IHD or MI) or CHF; the presence of cardiac pacing devices; history of AFib or arterial flutter; treatment with drugs that can change the appearance of the ECG; hydroelectrolytic disorders that can change the appearance of the ECG; chronic kidney disease; a period greater than 24 hours from the onset of symptoms until transfer to the University Emergency Hospital of Bucharest.

From a total of 335 patients, a total of 92 patients were excluded: 65 patients with traumatic SAH etiology and 27 patients due to other exclusion criteria. The study thus includes a total of 243 patients with non-traumatic SAH. Among them, 203 had an SAH of aneurysmal etiology, and 40 had a non-aneurysmal SAH etiology (26 patients with perimesencephalic SAH, 6 patients with AVMs, 4 patients with brain tumors, 2 patients with ITP, 1 patient with anticoagulant overdose and 1 patient using cocaine).

Collected data: general data (age, sex, environment of origin), PPA, pre-existing treatment, neurological and cardiovascular clinical data, paraclinical data (brain imaging, ECG, hsTnIc, NT-proBNP, echocardiography), type of treatment, as well as in-hospital evolution (death/discharge/neurological complications).

Statistical data processing was performed using Microsoft Excel 16 and IBM SPSS Statistics v20. Data were presented using means, medians, inter-quartiles, or percentages for categorical data, and differences between groups were analyzed using parametric or non-parametric tests. Among the non-parametric tests used, we mention Mann-Whitney for evaluation based on median values, Spearman rho for correlations, Chi-square tests for evaluations of independence between 2 sets of categorical data. Odds Ratio was also used to determine the predictive quality of some data sets.

5. Results

The entire group, of 243 patients with non-traumatic SAH, had the following general characteristics: the majority (53.1%) was represented by women (129 patients); mean age was 51.41 ± 12 years; 8 GCS points (median) at hospital admission; 11 days median length of hospitalization; most (64.2% of them) were hospitalized for at least one day in the ATI (156 patients); 1 day median length of hospitalization in ATI; the majority (53.5% of them) died during hospitalization (130 patients).

Comparatively, the 2 subgroups, aneurysmal SAH versus non-aneurysmal SAH: majority women versus men; the same average and median age; greater severity of aneurysmal SAH: 8 versus 12 GCS points at admission, 9 versus 18.5 days median hospitalization (they died faster); although both had a median of 1 day of hospitalization in the ATI, a higher percentage of those with aneurysmal SAH requiring admission to the ATI; most died versus discharged.

The majority of patients with aneurysmal SAH (28.5% and 50% of them, respectively) had 5 GCS points and a Hunt and Hess V score at hospital admission, compared to 15 GCS points and a Hunt and Hess II score for the majority represented by 35 %, respectively 50% of patients with non-aneurysmal SAH. The higher severity of disease in patients with aneurysmal rupture was also evidenced by the higher Fisher scale score as well as the intracerebral extension of bleeding – more patients with aneurysmal SAH had a Fisher score of 4 and intracerebral, intraventricular, and deviation of midline compared to those with non-aneurysmal SAH.

The same favorable situation for patients with non-aneurysmal SAH was also reflected by the lack of neurological complications for most of them (70% of patients), with 30% of them developing symptomatic vasospasm, while, for patients with aneurysmal SAH, the situation of been opposite; only 22% of them had no neurological complications, while the majority, represented by 77.83% of them, developed vasospasm.

5.1. Cardiovascular parameters

For patients with nontraumatic SAH, as well as for those with aneurysmal SAH and non-aneurysmal SAH included in the study, the medians for systolic BP, mean BP, and AV were similar on all 3 days: 130-135 mmHg, 90-105 mmHg, and 80 -85 bpm. The fact that these medians did not differ statistically significantly between the 2 subgroups of patients with non-traumatic SAH in any of the first 3 days suggests that the ECG, cardiac enzyme, and echocardiographic changes are not due to an offer and demand imbalance, through

cardiac hypoperfusion, reinforcing the hypothesis that these changes are of neurogenic etiology, through diffuse myocardial damage, secondary to sympathetic activation.

The percentage of patients requiring vasopressor support was the highest on the first day of hospitalization (compared to the following 2 days) for the subgroup of patients with aneurysmal SAH (20.2%) and reached statistical significance for patients with aneurysmal SAH compared to patients with non-aneurysmal SAH.

Regarding the value of the hypoxemia index, for the subgroup of patients with aneurysmal SAH, its median value decreased gradually, from the first to the third day of hospitalization (from 290 mmHg to 244 mmHg), while the subgroup of patients with non-aneurysmal SAH, its median value increased slightly on the third day compared to the first (from 371 mmHg to 386 mmHg).

These statistically significant differences in the higher need for vasopressor support, as well as a higher level of pulmonary injury (most likely of neurogenic origin) for the subgroup of patients with aneurysmal SAH, further suggest the higher severity of the clinical outcome of these patients compared to the subgroup of patients with non-aneurysmal SAH.

5.2. ECG changes

In the study group, 78.18% (on the first day of hospitalization) and 83.5% (on the third day of hospitalization) of the patients with ECGs available for analysis presented ECG morphological changes. These results are due to the subgroup of patients with aneurysmal SAH. Therefore, the ECG abnormalities appeared early in the evolution of SAH, they were already present on most of the ECG traces obtained at the time of the patient's presentation to the emergency room, and they persisted for more than 3 days from the time of admission to the hospital. These results are in agreement with those presented in the literature, where these types of ECG abnormalities are described in percentages between 25% and 100%.

These morphologic abnormalities were diagnosed as being of neurogenic etiology, as they were interpreted as newly occurring ECG changes, in patients with an acute intracranial event and no known preexisting cardiac involvement, and patients with any type of preexisting ECG change were excluded from the study , as well as those with known heart disease. Another justification of the neurogenic etiology of the changes identified in the electrocardiogram of patients with non-traumatic SAH is the fact that they can be considered to have been asymptomatic, and discovered incidentally, in general, through a routine investigation in all patients presenting to the emergency room and not due to a specific

clinical indication (as in the case of investigations carried out for the diagnosis of an acute coronary event, when the clinical indication exists – anginal pain)

Ventricular extrasystoles were detected in 30% of patients with aneurysmal SAH. An important percentage of patients presented sinus tachycardia-type rhythm disturbances – between 30% and slightly over 40% of patients with spontaneous SAH, the majority being traced, again, by the subgroup of patients with aneurysmal SAH. More patients with aneurysmal SAH had sinus bradycardia compared to patients with non-aneurysmal SAH (12.76%).

This predominance of rhythm disturbances, as well as of ECG morphological ones among patients with aneurysmal SAH, suggests the important neurological component in the development of these electrocardiographic changes, a neurological component well known to be more important in the neuro-cardiac storm that occurs following an aneurysmal rupture.

The results obtained for the subgroup of patients with aneurysmal SAH are consistent with those described in the literature. From the ECG data available for these patients, during the first 3 days of hospitalization, it was observed that non-specific ST-T segment changes were the most frequently encountered types of ECG morphological changes (more than 40% of patients still hospitalized, on each of the days), followed by prolongation of the QTc interval (between 26 and 30% of patients still hospitalized) and the presence of a negative T wave (between 15 and 38% of patients still hospitalized). In addition, prolonged QTc interval has been described predominantly in females.

For patients with aneurysmal SAH, tachycardia, the development of life-threatening arrhythmias, the presence of ventricular extrasystoles, a prolonged QTc interval, as well as ST segment elevation were statistically significantly more frequent in patients who died in-hospital, compared to those who survived and were discharged. These ECG rhythm or morphological disturbances thus become unfavorable prognostic factors, being associated with in-hospital mortality. Moreover, after adjusting for age and sex, the value of the QTc interval was found to be an independent risk factor for in-hospital death.

On the other hand, tachycardia, ESV, as well as ST segment depression were statistically significantly more frequently described in patients who were not diagnosed with symptomatic vasospasm. This apparent discrepancy between the association of these ECG changes with mortality, but at the same time with the non-development of vasospasm can be explained by the fact that, in the case of the present thesis, it was symptomatic vasospasm, which was actively sought and diagnosed only for patients that were not in critical, comatose,

condition. Thus, in fact, the actual total number of patients who experienced vasospasm was unknown.

5.3. Cardiac troponin I

The median maximum value of hsTnIc was 0.98 ng/ml, therefore a moderate increase, (neurogenic etiology) and is a predictor of the severity and mortality of spontaneous SAH, together with the TnI values of the first 2 days: values directly proportional to the length of hospitalization in ATI and inversely proportional to the duration of hospitalization.

This conclusion was then confirmed by comparing median hsTnIc values between patients with spontaneous SAH who were discharged and those who died in-hospital: hsTnIc was at least 2-fold higher in patients who died compared to those who survived hospitalization, this difference being statistically significant both for the maximum value of hsTnIc and for the individual values, from the first 3 days of hospitalization.

These peak values of hsTnIc were recorded on the second day of hospitalization for patients who survived and on the third day for those who died during hospitalization, both for the entire group of patients with spontaneous SAH, as well as for the subgroup of patients with aneurysmal SAH.

An extremely important result of the thesis is the establishment, by applying a linear regression, of a relationship between the mortality rate and the maximum values of hsTnIc. We thus observed a strong relationship between peak hsTnIc and mortality, with each one-unit (1 ng/mL) increase in peak hsTnIc being associated with a 15.85% increase in mortality.

Another equally important result is the establishment of a hsTnIc threshold (which was found to be identical for patients with spontaneous SAH and those with aneurysmal SAH) above which mortality reaches 95% (1.32 ng/mL), as well as one from which mortality becomes 100% (2.38 ng/mL). These relatively low-moderate values of hsTnIc, from which the mortality of patients with SAH increases rapidly, confirm, once more, the neurogenic mechanism of producing cardiac dysfunction among this category of patients.

In the present paper, the clinical and paraclinical predictors of increased cardiac TnI values described in the literature are confirmed: loss of consciousness at the time of subarachnoid bleeding, poor clinical status (expressed by the existence of coma or a high Hunt and Hess score - IV/V at admission in the hospital), large extent of bleeding revealed on native CT (high Fisher grade - 4/5), presence of intracerebral or intraventricular bleeding, cerebral edema (expressed as midline deviation), as well as tachycardia.

5.4. NT-proBNP

The thesis confirmed the data from the literature, according to which, in patients with aneurysmal SAH and increased NT-proBNP, the most frequent location of the ruptured aneurysm is at the AcoA level, and that an increased serum value of NT-proBNP is a predictor of early, in-hospital mortality. This remained true after adjusting for age and sex.

5.5. Echocardiographic changes

Once again, patients with aneurysmal SAH had a higher incidence of echocardiographic changes compared to those with non-aneurysmal SAH, a result that presented statistical significance. This strengthens the diagnosis of the neurogenic origin of the cardiac dysfunction among this subgroup of patients, even though the reversibility of these changes in myocardial kinetics could not be demonstrated, given that the patients included in the study did not have echocardiography repeated more than 7 days after rupture of the aneurysm, that would have been used to describe the evolution of those cardiac changes observed early by ultrasound, most frequently on the day of the patients admission to the hospital, i.e. in the first 24-48 hours from the moment of the aneurysm rupture.

Moreover, for this subgroup of patients, evolving unfavorably, there is a predictor quality in both the development of LV systolic dysfunction (with LVEF less than or equal to 50%), versus a high mortality rate, and in the diagnosis of diastolic dysfunction versus patient survival and discharge (inversely correlated with in-hospital mortality).

6. Conclusions and personal contributions

An increased value of TnI is associated with a dismal prognosis: neurological and cardiovascular complications, long duration of hospitalization in the ICU, as well as with a high in-hospital mortality.

High levels of NT-proBNP have found to be also associated with early in-hospital death which leads to the conclusion that serum levels of troponin and NT-proBNP should be routinely determined upon admission to the hospital, and then monitored dynamically, for a better orientation of prognosis and management decisions.

It is also essential to differentiate ischemic (potentially irreversible) from neurogenic (reversible) cardiac injury in patients with nontraumatic SAH.

Proposed monitoring protocol: On admission, an ECG trace as well as serum TnI and NT-proBNP should be routinely determined. In case of any changes, it is recommended to perform an echocardiography, as well as the dynamic follow-up of the 2 cardiac markers, by repeating them on days 2 and 3. Also, in patients with a severe spontaneous SAH, a continuous telemetric monitoring is indicated, at least until the neural injury stabilizes.

Regarding personal contributions, I have carried out a study for the first time, at national level, describing a current topic of great interest, through a multidisciplinary approach, with concepts of neurosurgery, cardiology and intensive therapy. The pathology in question represents a complex public health problem, with a significant socio-economic impact.

We demonstrated that the obtained results replicate those in the literature, so I was able to consolidate the already existing information and confirm that the internationally recommended management can be safely implemented at the national level.

We had a particular interest in anesthetic risk assessment, in order to take measures that reduce cardiac risk, such as avoiding strong myocardial depressant anesthetics, ensuring an optimal level of oxygenation and possible invasive monitoring of spontaneous SAH patients with cardiac dysfunction of neurogenic origin.

In addition, we have demonstrated that troponin is extremely useful in perioperative risk assessment, which can be used to justify certain aggressive interventions, or, conversely, to limit therapeutic support.

Bibliografie

1. van Gijn J., Rinkel G.J. Subarachnoid haemorrhage: diagnosis, causes and management, *Brain: a journal of neurology*, 124, Pt 2, 249–278, 2001

2. van Gijn J., Kerr R.S. et al. Subarachnoid haemorrhage, *Lancet*, 369, 9558, 306–318, 2007

3. Armin S.S., Colohan A.R.T. et al. Traumatic subarachnoid hemorrhage: our current understanding and its evolution over the past half century, *Neurol Res*., 28, 445-452, 2006

4. Rinkel G.J., Van Gijn J. et al. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes, *Stroke*, 24, 9, 1403–1409, 1993

5. Anderson T. Current and Evolving Management of Subarachnoid Hemorrhage, *Crit Care Nurs Clin North Am*., 21, 529-539, 2009

6. Connolly E.S., Rabinstein A.A. et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association, *Stroke*, 43, 6, 1711–1737, 2012

7. Suarez J.I., Diagnosis and Management of Subarachnoid Hemorrhage, *Continuum (Minneapolis, Minn.) Neurocritical Care*, 21, 5, 1263–1287, 2015

8. Cross D.T., Tirschwell D.L. et al. Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states, *Journal of neurosurgery*, 99, 5, 810–817, 2003

9. Josephson S.A., Douglas V.C. et al. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management, *J Neurosurg*., 112, 3, 626-630, 2010

10. Dringer M.N., Bleck T.P. et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference, *Neurocritical care*, 15, 2, 211–240, 2011

11. McNeill L., English S.W. et al. Effects of institutional caseload of subarachnoid hemorrhage on mortality: a secondary analysis of administrative data, *Stroke*, 44, 3, 647–652, 2013

12. Rinkel G.J., Wijdicks E.F. et al. Outcome in patients with subarachnoid haemorrhage and negative angiography according to pattern of haemorrhage on computed tomography, *Lancet*, 338, 8773, 964–968, 1991

13. Rinkel G.J., Wijdicks E.F. et al. The clinical course of perimesencephalic nonaneurysmal subarachnoid hemorrhage, *Annals of neurology*, 29, 5, 463–468, 1991

14. Ildan F.,Tuna M. et al. Prognosis and prognostic factors in nonaneurysmal perimesencephalic hemorrhage: a follow-up study in 29 patients, *Surgical neurology*, 57, 3, 160–165; discussion 165-166, 2002

15. Brilstra E.H., Hop J.W. et al. Quality of life after perimesencephalic haemorrhage, *J Neurol Neurosurg Psychiatry*., 63, 3, 382-384, 1997

16. Marquardt G., Niebauer T. et al. Long term follow up after perimesencephalic subarachnoid haemorrhage, *Journal of neurology, neurosurgery, and psychiatry*, 69, 1, 127–130, 2000

17. Kopelnik A., Zaroff J.G. Neurocardiogenic injury in neurovascular disorders, *Critical care clinics*, 22, 4, 733–752, 2006

18. Krisnamoorthy V., Mackensen G.B. et al. Cardiac Dysfunction After Neurologic Injury: What Do We Know and Where Are We Going?, *Chest*, 149, 5, 1325–1331, 2016

19. Prasad Hrishi A., Ruby Lionel K. et al. Head Rules Over the Heart: Cardiac Manifestations of Cerebral Disorders, *Indian journal of critical care medicine*, 23, 7, 329–335, 2019

20. Ripoll J.G., Blackshear J.L. et al. Acute Cardiac Complications in Critical Brain Disease, *Neurologic clinics*, 35, 4, 761–783, 2017

21. Nagai M.,Hoshide S. et al. The insular cortex and cardiovascular system: a new insight into the brain-heart axis, *Journal of the American Society of Hypertension: JASH*, 4, 4, 174–182, 2010

22. Grunsfeld A., Fletcher J.J. et al. Cardiopulmonary complications of brain injury, *Current neurology and neuroscience reports*, 5, 6, 488–493, 2005

23. Manea M.M., Comsa M. et al. Brain-heart axis–Review Article, *Journal of medicine and life*, 8, 3, 266–271, 2015

24. Stevens R.D., Nyquist P.A. The systemic implications of aneurysmal subarachnoid hemorrhage, *Journal of the neurological sciences*, 261, 1-2, 143–156, 2007

25. Wittstein I.S. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning?, *Cellular and molecular neurobiology*, 32, 5, 847–857, 2012

26. Pereira V.H., Cerqueira J.J. et al. Stressed brain, diseased heart: a review on the pathophysiologic mechanisms of neurocardiology, *International journal of cardiology*, 166, 1, 30–37, 2013

27. Prunet B., Basely M. et al. Impairment of cardiac metabolism and sympathetic innervation after aneurysmal subarachnoid hemorrhage: a nuclear medicine imaging study, *Critical care*, 18, 3, R131, 2014

28. Dous G.V., Grigos A.C. et al. Elevated troponin in patients with acute stroke - Is it a true heart attack?, *The Egyptian heart journal*, 69, 3, 165–170, 2017

29. Kagiyama N., Sugahara M. et al. Neurocardiac Injury Assessed by Strain Imaging Is Associated With In-Hospital Mortality in Patients With Subarachnoid Hemorrhage, *JACC. Cardiovascular imaging*, 13, 2 2, 535–546, 2020

30. Okabe T., Kanzaria M. et al. Cardiovascular protection to improve clinical outcomes after subarachnoid hemorrhage: is there a proven role?, *Neurocritical care*, 18, 2, 271–284, 2013

31. Salem R., Vallée F. et al. Subarachnoid hemorrhage induces an early and reversible cardiac injury associated with catecholamine release: one-week follow-up study, *Critical care*, 18, 5, 558, 2014

32. Huang W.J., Chen W.W., et al. Comparison of cerebral-cardiac syndrome caused by nonaneurysmal or aneurysmal subarachnoid hemorrhage, *European review for medical and pharmacological sciences*, 18, 24, 3737–3742, 2014

33. Garg R., Bar B. Systemic Complications Following Aneurysmal Subarachnoid Hemorrhage, *Current neurology and neuroscience reports*, 17, 1, 7, 2017

34. Lee V.H., Connolly M. et al. Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction, *Journal of neurosurgery*, 105, 2, 264–270, 2006

36. Sakr Y.L., Ghosn I. et al. Cardiac manifestations after subarachnoid hemorrhage: a systematic review of the literature, *Progress in cardiovascular diseases*, 45, 1, 67–80, 2002

37. Naval N.S., Stevens R.D. et al. Controversies in the management of aneurysmal subarachnoid hemorrhage, *Critical care medicine*, 34, 2, 511–524, 2006

38. Bruder N., Rabinstein A. Cardiovascular and Pulmonary Complications of Aneurysmal Subarachnoid Hemorrhage, *Neurocrit Care*, 15, 2, 257-269, 2011

39. Zahid T., Eskander N. et al. Cardiac Troponin Elevation and Outcome in Subarachnoid Hemorrhage, *Cureus*, 12, 8, e9792, 2020

40. Parekh N., Venkatesh B. et al. Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage, *Journal of the American College of Cardiology*, 36, 4, 1328–1335, 2000

41. Oras J., Grivans C. 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, *Neurocritical care*, 23, 2, 233–242, 2015

42. Behrouz R., Sullebarger J.T. et al. Cardiac manifestations of subarachnoid hemorrhage, *Expert Rev Cardiovasc Ther*., 9, 3, 303-307, 2011

43. Zhang L.,Wang Z. et al. Cardiac Troponin Elevation and Outcome after Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis, *Journal of stroke and cerebrovascular diseases*, 24, 10, 2375–2384, 2015

44. Bender M., Stein M. et al. Serum Cortisol as an Early Biomarker of Cardiopulmonary Parameters Within the First 24 Hours After Aneurysmal Subarachnoid Hemorrhage in Intensive Care Unit Patients, *J Intensive Care Med*., 35, 11, 1173-1179, 2020

45. Mavridis L.N., Meliou M. et al. Troponin elevation in subarachnoid hemorrhage, *Journal of Acute Disease*, 4, 1, 7-11, 2015

46. Oras J., Grivans C. et al. Elevated high-sensitive troponin T on admission is an indicator of poor long-term outcome in patients with subarachnoid haemorrhage: a prospective observational study, *Critical care*, 20, 11, 2016

47. McAteer A.,Hravnak M. et al. The Relationships Between BNP and Neurocardiac Injury Severity, Noninvasive Cardiac Output, and Outcomes After Aneurysmal Subarachnoid Hemorrhage, *Biological research for nursing*, 19, 5, 531–537, 2017

48. Norberg E., Odenstedt-Herges H. et al. Impact of Acute Cardiac Complications After Subarachnoid Hemorrhage on Long-Term Mortality and Cardiovascular Events, *Neurocritical care*, 29, 3, 404–412, 2018

49. van der Bilt I.A.C., Hasan D. et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis, *Neurology*, 72, 7, 635–642, 2009

50. Maeder M., Fehr T. et al. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides, *Chest*, 129, 5, 1349–1366, 2006

51. Duello K.M., Nagel J.P. et al. Relationship of Troponin T and Age- and Sex-Adjusted BNP Elevation Following Subarachnoid Hemorrhage with 30-Day Mortality, *Neurocritical care*, 23, 1, 59–65, 2015

52. Chou S.H.Y., Macdonald R.L. et al. Biospecimens and Molecular and Cellular Biomarkers in Aneurysmal Subarachnoid Hemorrhage Studies: Common Data Elements and Standard Reporting Recommendations, *Neurocrit Care*, 30, 46-59, 2019

53. Sviri G.E., Feinsod M. et al. Brain natriuretic peptide and cerebral vasospasm in subarachnoid hemorrhage. Clinical and TCD correlations, *Stroke*, 31, 1, 118–122, 2000

54. Sviri G.E., Shik V. et al. Role of brain natriuretic peptide in cerebral vasospasm, *Acta neurochirurgica*, 145, 10, 851–860, 2003

55. Bulsara K.R., McGirt M.J. et al. Use of the peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage, *J Neurosurg*., 98, 3, 524-528, 2003

56. Gupte M., John S. et al. Troponin elevation in subarachnoid hemorrhage does not impact in-hospital mortality, *Neurocritical care*, 18, 3, 368–373, 2013

57. Urbaniak K., Merchant A.I. et al. Cardiac complications after aneurysmal subarachnoid hemorrhage, *Surgical neurology*, 67, 1, 21–28, 2007

58. Dande A.S., Pandit A.S. Broken heart syndrome, neurogenic stunned myocardium and stroke, *Current treatment options in cardiovascular medicine*, 15, 3, 265–275, 2013

59. Malik A.N., Gross B.A. et al. Neurogenic Stress Cardiomyopathy After Aneurysmal Subarachnoid Hemorrhage, *World neurosurgery*, 83, 6, 880–885, 2015

60. Trio O., de Gregorio C., et al. Myocardial dysfunction after subarachnoid haemorrhage and tako-tsubo cardiomyopathy: a differential diagnosis?, *Therapeutic advances in cardiovascular disease*, 4, 2, 105–107, 2010

61. Bihorac A., Ozrazgat-Baslanti T. et al. Long-Term Outcomes for Different Forms of Stress Cardiomyopathy After Surgical Treatment for Subarachnoid Hemorrhage, *Anesth Analg*., 122, 5, 1594-1602, 2016

62. Ancona F., Bertoldi L.F. et al. Takotsubo cardiomyopathy and neurogenic stunned myocardium: similar albeit different, *Eur Heart J*., 37, 37, 2830-2832, 2016

63. Bender M, Stein M. et al. Troponin I as an Early Biomarker of Cardiopulmonary Parameters Within the First 24 Hours After Nontraumatic Subarachnoid Hemorrhage in Intensive Care Unit Patients, *J Intensive Care Med*., 35, 12, 1368-1373, 2020