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Original Article

Pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms: A systematic review

Benjamin W. Y. Lo, Hitoshi Fukuda[1], Yusuke Nishimura[2], R. Loch Macdonald[3], Forough Farrokhyar[4], Lehana Thabane[5], Mitchell A. H. Levine[6]

Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, [3]Division of Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, [4]Departments of Surgery, Clinical Epidemiology and Biostatistics and [5]Clinical Epidemiology and Biostatistics, McMaster University, [6]Department of Medicine, Clinical Epidemiology and Biostatistics, Division of Clinical Pharmacology, McMaster University, Hamilton, Canada, [1]Department of Neurosurgery, Kurashiki Central Hospital, University of Kyoto, Okayama, [2]Department of Neurosurgery, Nagoya University Hospital, Nagoya University, Nagoya, Japan

E-mail: *Benjamin W. Y. Lo - benjamin.lo@mcgill.ca; Hitoshi Fukuda - fukudaharpseal@gmail.com; Yusuke Nishimura - yusukenishimura0411@gmail.com; R. Loch Macdonald - macdonaldlo@smh.ca; Forough Farrokhyar - farrokh@mcmaster.ca; Lehana Thabane - thabanl@mcmaster.ca; Mitchell A. H. Levine - levinem@mcmaster.ca
*Corresponding author

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Abstract

Background: Patients with ruptured brain aneurysms and aneurysmal subarachnoid hemorrhage suffer neurological damage from primary injury of the aneurysm rupture itself, as well as a number of secondary injurious processes that can further worsen the affected individual's neurological state. In addition, other body systems can be affected in a number of brain-body associations.

Methods: This systematic review synthesizes prospective and retrospective cohort studies that investigate brain-body associations in patients with ruptured brain aneurysms. The methodologic quality of these studies will be appraised.

Results: Six cohort studies were included in this systemic review. The methodologic quality of each study was assessed. They had representative patient populations, clear selection criteria and clear descriptions of study designs. Reproducible study protocols with ethics board approval were present. Clinical results were described in sufficient detail and were applicable to aneurysmal subarachnoid hemorrhage patients in clinical practice. There were few withdrawals from the study. Limitations included small sample sizes and between-study differences in diagnostic tests and clinical outcome endpoints. Several pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms were clarified through this systematic review. Sympathetic activation of the cardiovascular system in aneurysmal subarachnoid hemorrhage not only triggers the release of atrial and brain natriuretic peptides it can also lead to increased pulmonary venous pressures and permeability causing hydrostatic pulmonary edema. Natriuretic states can herald the onset or worsening of clinical vasospasm as the renin-angiotensin-aldosterone system is activated in a delayed manner.

Conclusions: This systematic review synthesizes the most current evidence of underlying mechanisms of brain related associations with body systems in aneurysmal subarachnoid hemorrhage. Results gained from these studies

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are clinically useful and shed light on how ruptured brain aneurysms affect the cardiopulmonary system. Subsequent neuro-cardio-endocrine responses then interact with other body systems as part of the secondary responses to primary injury.

Key Words: Aneurysmal subarachnoid hemorrhage, brain-body interactions, cardiopulmonary interactions, neuro-cardio-endocrine interactions, systematic review

INTRODUCTION

Brain injury spectrum after aneurysmal subarachnoid hemorrhage

Patients with ruptured brain aneurysms and aneurysmal subarachnoid hemorrhage suffer neurological damage from primary injury of the aneurysm rupture itself, as well as a number of secondary injurious processes that can further worsen the affected individual's neurological state. Secondary injurious processes can be related to the nervous system such as re-bleeding from the ruptured aneurysm, brain swelling, occurrence of a delayed stroke, brain blood vessel vasospasm leading to seizures, strokes and an increase in brain-spinal fluid causing hydrocephalus. Figure 1 illustrates the spectrum of primary and secondary neurological injuries after subarachnoid hemorrhage.

Brain-body associations in aneurysmal subarachnoid hemorrhage

When brain aneurysms rupture, other body systems can be affected in a number of brain-body associations. Previous literature attempted to characterize cardiac and pulmonary manifestations in aneurysmal subarachnoid hemorrhage.[2] Aneursymal subarachnoid hemorrhage triggers catecholamine release resulting in:

1. Stunned myocardium and contraction band necrosis, and
2. Altered pulmonary capillary permeability and pulmonary edema.

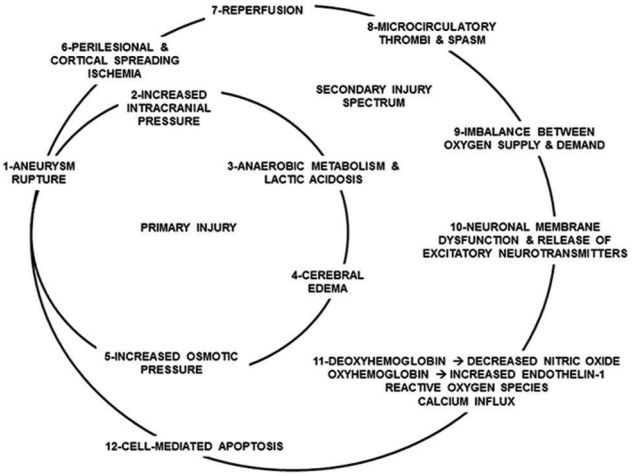
Yet, patients with ruptured brain aneurysms manifest clinical observations to show the involvement of other body organs including endocrine and renal abnormalities.

Objectives

The purpose of this systematic review was to synthesize studies that investigate the pathophysiologic mechanisms of brain-body associations in patients with ruptured brain aneurysms. This systematic review also critically appraises the methodologic quality of studies that attempt to derive brain-body associations in aneurysmal subarachnoid hemorrhage.

METHODS

This systematic review was designed based on a predefined protocol.



Explanations for each step are given below:

1. Rupture of a brain aneurysm,
2. Increased intracranial pressure results in decreased blood flow to the brain,
3. Metabolism under lack of oxygen leading to formation and release of lactic acid,
4. Brain swelling as a result of increased intracranial pressure and anaerobic metabolism,
5. Fluid leaks across disrupted blood-brain barrier,
6. Lack of blood flow and oxygen spread from site of aneurysm rupture to across the entire brain,
7. Injurious process when brain attempts to re-supply blood and oxygen to involved areas,
8. Clotting is triggered in small vessels, along with induced constriction of vessels of different sizes (vasospasm),
9. Not enough oxygen is supplied via brain blood flow to meet the metabolic requirements of the damaged brain areas,
10. Nerve cell membranes are disrupted, and further damage is caused with release of a number of chemicals that are toxic to the injured regions,
11. Products (including reactive oxygen species, endothelin-1, decreased nitric oxide, calcium) trigger deleterious processes (such as seizures, vasospasm, delayed strokes), and
12. The process of programed cell death is triggered.

Figure 1: Spectrum of primary and secondary neurologic injuries after aneurysmal subarachnoid hemorrhage

Study eligibility criteria

Studies that were eligible for this systematic review included:

1. Studies of adult patients with ruptured brain aneurysms,
2. These patients received diagnostic tests to investigate pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage,
3. These patients also received reference standard investigations to document multi-organ deteriorations after brain aneurysm rupture, and
4. Prospective and retrospective cohort studies and randomized controlled trials investigating pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage.

We excluded the following studies:

1. Those that do not characterize pathophysiologic mechanisms of brain-body associations,
2. Those that do not distinguish between aneurysmal and nonaneurysmal subarachnoid hemorrhage, and
3. Studies based on expert opinions.

Eligible studies were limited to those published from January 1, 2000 to March 31, 2014. We truncated eligible studies to this time period because of advancements in:

1. Investigations to diagnose aneurysmal subarachnoid hemorrhage, such as computed tomography (CT) angiogram,
2. Diagnostic tests to investigate pathophysiologic mechanisms of brain-body associations, such as advanced pulse contour analysis for cardiopulmonary parameters and blood assays for neuroendocrine markers, and
3. Surgical and neurocritical care treatment differences such as availability of minimally invasive endovascular techniques.

Literature search

Two reviewers (Benjamin Lo [BL], Hitoshi Fukuda [HF]) independently searched a number of electronic databases. Relevant studies were identified from Ovid MEDLINE, Ovid EMBASE, Web of Science, the Cumulative Index to Nursing and Allied Health Literature, without language restrictions. To include gray literature, we also searched Proceedings First and Papers First. We used the following combination of search terms:

1. "Aneurysmal subarachnoid hemorrhage" and "cardiopulmonary,"
2. "Aneurysmal subarachnoid hemorrhage" and "renal,"
3. "Aneurysmal subarachnoid hemorrhage" and "gastrointestinal,"
4. "Aneurysmal subarachnoid hemorrhage" and "immune" and "hematologic,"
5. "Aneurysmal subarachnoid hemorrhage" and "brain-body associations."

Study selection and data collection process

Both investigators (BL and HF) reviewed all titles and abstracts, and full reports of all potentially relevant trials. The initial literature search (January 1, 2000–March 31, 2014) yielded 150 citations [Figure 2]. Screening by title and abstract and citation yielded 88 items. Of these 88 items, reviewers BL and HF reached agreement on 41 items for inclusion, 38 items for exclusion and were unsure on 9 items. A consensus conference was held with the assistance of a third reviewer, Yusuke Nishimura (YN). Interrater reliability was high (estimated kappa 0.81 [95% (CI) 0.76–0.87] for citation and abstract screening). Fifty full text articles were identified as potentially relevant, and were assessed, with further exclusion of articles due to:

1. Inappropriate patient inclusion and exclusion criteria,
2. Inadequate outcome reporting, and
3. Discussions are lacking pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage.

Investigators BL and HF then independently applied the inclusion criteria to the full reports. Each trial report was examined carefully for its methodologic quality. As outlined in the "methodologic quality assessment" section, each article was appraised in nine areas. Of the 54 items assessed in six articles, BL and HF reached agreement on 43 items, disagreed on 8 items and were unsure on 3 items (kappa statistic = 0.82, 95% CI 0.71–0.93). Disagreements were resolved through consensus discussions and YN, the third reviewer.

For data collection, the reviewers (BL, HF) extracted relevant data using a data extraction form, piloted on a sample of included studies. Disagreements were resolved by consensus discussions and YN, the third reviewer.

Assessment of pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage

For this systematic review, the following items were reviewed in order to clarify pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage:

1. Study design – including description of study protocol, study setting, and recruitment,
2. Patient population – including representative of cohort, inclusion and exclusion criteria, and sample size,
3. Investigations – including reference tests to document organ dysfunction and diagnostic tests to document how ruptured brain aneurysms affect other organs,
4. Outcome – including discussions on pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage, and
5. Ethical conduct of study – including institutional ethics board approval and funding declarations.

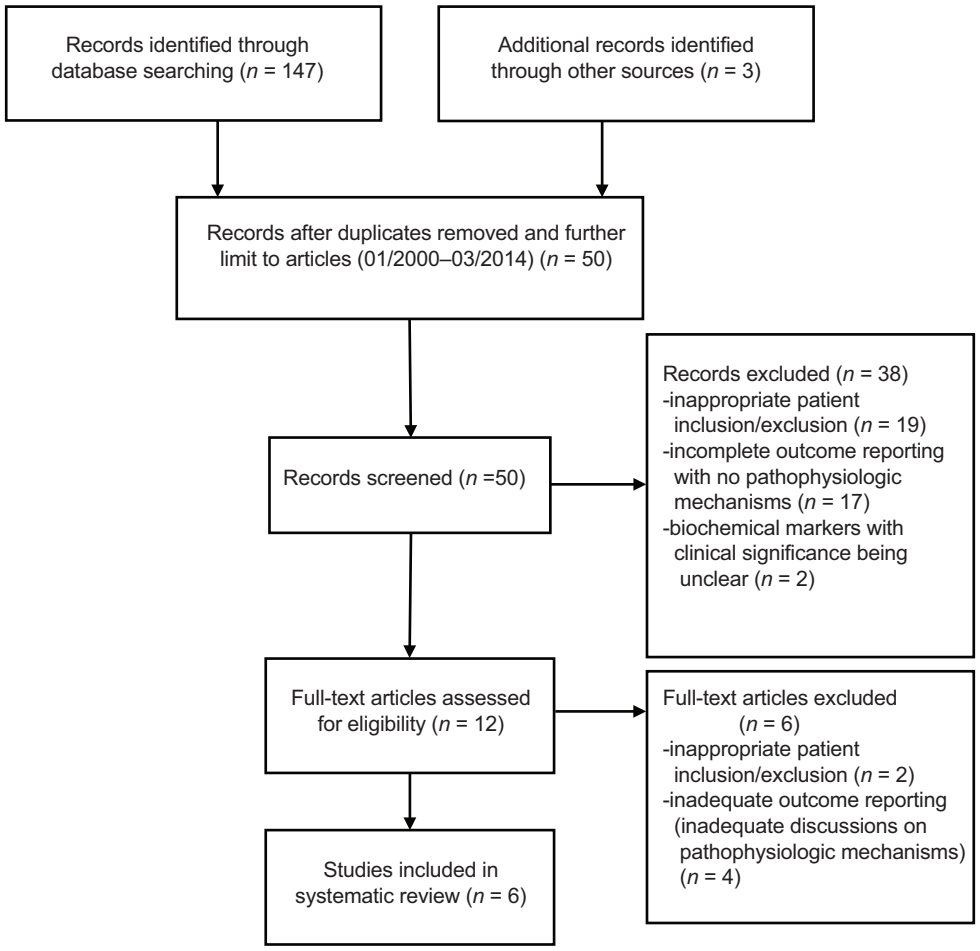


Figure 2: Flow diagram of study selection

Methodologic quality assessment

For this systematic review, we sampled the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies Tool– Revised Version).[12] The following areas were used in methodologic quality assessment as they would apply to pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage:

1. Whether subjects included are representative of those treated in clinical practice,
2. Clear study designs and descriptions of study protocols, inclusion and exclusion criteria, study settings, and recruitment,
3. Inclusion of study findings with adequate discussions of pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage,
4. Clear descriptions of reference standards to document multi-organ dysfunction,
5. Whether diagnostic tests to investigate, brain-body associations were described in sufficient detail to permit test replication,
6. Whether clinical data for study subjects are reproducible for those treated in clinical practice,
7. Reporting of noninterpretable test results,
8. Explanation of study withdrawals, and
9. Whether the measure is clinically useful.

RESULTS

Study search and selection

The initial literature search (January 1, 2000 – March 31, 2014) yielded 150 citations [Figure 2]. These were screened by title and abstract. Fifty full text articles were identified as potentially relevant, and were assessed, with further exclusion of articles due to inappropriate patient inclusion and exclusion criteria, inadequate outcome reporting, and discussions lacking pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage. Six studies were included in this systemic review.

A meta-analysis was not feasible in this review to statistically pool outcomes obtained from the included studies clarifying pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms. Marked between-study differences was noted in the included studies with: (1) Differing diagnostic tests and reference value ranges, (2) differing clinical outcome endpoint measures, and (3) scarcity of studies

investigating each type of diagnostic investigation. Diagnostic tests of serum and cerebrospinal fluid markers were studied in four out of six studies, radiographic investigations in two out of six studies, and invasive pulmonary artery thermodilution parameters in two out of six studies. In addition, there is no standardization of diagnostic tests between investigating centers.

Study results and synthesis of results

This systemic review identified five prospective cohort studies and one retrospective study for inclusion in the analysis. Of the six methodologically rigorous studies identified for this systematic review, pathophysiologic mechanisms were clarified between the brain and the following organ systems:

1. Cardiac system – six out of six studies,
2. Pulmonary system – three out of six studies,
3. Endocrine system – three out of six studies,
4. Renal system (including electrolyte and fluid balance) – three out of six studies,
5. Immune and hematologic systems – zero studies, and
6. Gastrointestinal system – zero studies.

Assessment of pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage for included studies

Article 1: Endocrine response after severe subarachnoid hemorrhage related to sodium and blood volume regulation

In this prospective cohort study, Audibert *et al.* investigated endocrinologic responses, as well as sodium and water regulation after severe aneurysmal subarachnoid hemorrhage.[1] Over a period of 2 years, 19 adults with aneurysmal subarachnoid hemorrhage were included (average 47 years old). Totally, 12 patients were excluded because of the history of renal insufficiency, cardiac disease, chronic treatment with diuretics, angiotensin-converting enzyme inhibitors, and steroids. Clear study protocols were described with the maintenance of euvolemia and sodium balance. Reference standard tests that documented multi-organ involvement included an electrocardiogram, cardiac enzymes, echocardiography, and transcranial Doppler ultrasound. Diagnostic tests performed to clarify brain-body associations included daily sodium excretion fraction, glomerular filtration rate, creatinine clearance, plasma levels of brain natriuretic peptide, atrial natriuretic peptide, aldosterone, renin, angiotensin II, and vasopressin. This study found the following:

1. With maintenance of euvolemia and salt balance, only 1 out of 19 patients experienced severe clinical vasospasm,
2. Levels of brain natriuretic peptide increased between days 1 and 3 after aneurysmal rupture,
3. Levels of atrial natriuretic peptide increased between days 4 and 6 after aneurysmal rupture, with associated increases in levels of renin, aldosterone and angiotensin II, and
4. Levels of vasopressin increased between days 10 and 12 after aneurysmal rupture.

This study clearly describes the relationship between brain aneurysmal rupture and delayed activation of the renin-angiotensin-aldosterone system. It had institutional ethics board approval, and clear declaration of funding sources. However, its main weaknesses included small study sample size, patient selection, and center referral biases.

Article 2: Neuro-cardio-endocrine response to acute subarachnoid hemorrhage

In this prospective cohort study, Espiner *et al.* investigated relationships between neurologic cardiac and endocrine responses after severe aneurysmal subarachnoid hemorrhage.[5] Over a period of 2 years, 18 adults with aneurysmal subarachnoid hemorrhage were included (average 54 years old). Exclusion criteria included the history of renal, hepatic, cardiac, endocrine diseases, and the history of diuretic and angiotensin converting enzyme inhibitor use prior to hospitalization. Clear study protocols were described. Patients were prescribed tapering dose of dexamethasone on admission. Reference standard tests that documented multi-organ involvement included an electrocardiogram, cardiac enzymes, chest radiographs. Diagnostic tests performed to clarify brain-body associations included plasma levels of cardiac enzymes, endothelin, brain natriuretic peptide and atrial natriuretic peptide, cerebrospinal fluid levels of brain natriuretic peptide, and atrial natriuretic peptide. This study found the following:

1. Brain natriuretic peptide and atrial natriuretic peptide levels in plasma increased in the first 3 days postaneurysmal rupture. They returned to normal levels by day 7. Cerebrospinal fluid levels of brain natriuretic peptide and atrial natriuretic peptide did not show any changes. Abnormal electrocardiograms were noted in 6 out of 7 patients
2. Urinary sodium levels increased within the first 3 days then remained stable. Plasma sodium levels gradually decreased
3. Plasma vasopressin levels were increased on presentation then fell to normal levels after 2 days. Plasma aldosterone and renin levels increased at day 10–12. Cortisol levels fell abruptly on day 3 and maintained low levels to day 10
4. Initial elevations of epinephrine, norepinephrine, and endothelin fell by day 3 and remained at subnormal levels.

This study thoroughly describes the various relationships between the brain, neuroendocrine and renal systems. It had institutional ethics board approval and clear declaration of funding sources. However, its main

weakness is the treatment of patients with admission dose of dexamethasone which further delayed activation of the renin-angiotensin-aldosterone system. Patients also demonstrated depressed adrenal-hypothalamic cortisol axis. This study also had small study sample size. Other weaknesses included patient selection and center referral biases.

Article 3: Subarachnoid hemorrhage complicated with neurogenic pulmonary edema and takatsubo-like cardiomyopathy

In this retrospective cohort study, Inamasu *et al.* characterized cardiopulmonary dysfunctions in aneurysmal subarachnoid hemorrhage.[6] Over a period of 5 years, 16 adults with aneurysmal subarachnoid hemorrhage and neurogenic pulmonary edema were included (average 63 years). Exclusion criteria included patients with nonaneurysmal subarachnoid hemorrhage. Clear study protocols were described. Patients were maintained euvolemic and had spinal catheters for clot clearance. Reference standard tests included electrocardiogram and chest radiograph. Diagnostic tests included a transthoracic echocardiogram. This study found the following:

1. Of 16 patients with neurogenic pulmonary edema, 14 had takatsubo-like cardiomyopathy. All exhibited electrocardiographic changes (including ST segment abnormalities, QT prolongation, and T-wave inversions). They were all intubated and were on vasopressors
2. Neurogenic pulmonary edema was significantly associated with posterior circulation aneurysms ($P = 0.004$). 9 out of 16 patients died (7 from the primary aneurysmal rupture, 1 from rebleeding and 1 from vasospasm-induced strokes).

This study clearly demonstrated relationships between neurogenic pulmonary edema and takotsubo-like cardiomyopathy. It had institutional ethics board approval, and clear declaration of funding sources. However, its main weaknesses included small study sample size, patient selection, and center referral biases.

Article 4: Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage

In this retrospective cohort study, Naidech *et al.* investigated relationships between cardiac troponin rise after aneurysmal subarachnoid hemorrhage and its association with cardiopulmonary complications, delayed cerebral ischemia and death.[7] Over a period of 4 years, 253 patients with subarachnoid hemorrhage and electrocardiographic abnormalities were included (average 55 years). Exclusion criteria included patients with traumatic subarachnoid hemorrhage and hemorrhage from arteriovenous malformations. Clear study protocols were described. Patients were maintained euvolemic. Reference standard tests included an electrocardiogram. Diagnostic tests included cardiac enzymes and chest radiographs. This study found the following:

1. Cardiac enzyme elevation was noted in patients who were older (average age 55 years), worse admission neurologic status, more blood on CT scan on admission, more physiologic dysfunction, and hypertensive history
2. Cardiac enzyme elevation was associated with risk of hypotension requiring vasopressors, left ventricular systolic dysfunction on echocardiogram, delayed cerebral ischemia from vasospasm and death.

This study demonstrated associations between cardiac troponin elevation and cardiovascular-related morbidity and mortality after aneurysmal subarachnoid hemorrhage. It had institutional ethics board approval, and clear declaration of funding sources. However, this study did not distinguish between aneurysmal and nonaneurysmal subarachnoid hemorrhage. Furthermore, it did not discuss pathophysiologic mechanisms of brain-body associations in detail.

Article 5: Clinical significance of elevated natriuretic peptide levels and cardiopulmonary parameters after subarachnoid hemorrhage

In this prospective cohort study, Nakamura *et al.* investigated the relationships between natriuretic peptides and changes in cardiopulmonary parameters.[10] Over a period of 2 years, 20 adults with aneurysmal subarachnoid hemorrhage were included (average 65 years). Exclusion criteria included patients with a history of acute myocardial infarction, arrhythmia, and congestive heart failure. Clear study protocols were described. Patients were maintained euvolemic. Reference standard tests included electrocardiograph, chest radiograph, echocardiogram, and transcranial Doppler. Diagnostic tests included plasma levels of atrial natriuretic peptide and brain natriuretic peptide, and pulse contour analysis to measure cardiopulmonary parameters. This PiCCO system measured cardiac index, systemic vascular resistance index, intrathoracic blood volume index, and extravascular lung water index. This study found the following:

1. Plasma levels of brain natriuretic peptides peaked on postaneurysm rupture day 1. Plasma levels of atrial natriuretic peptide peaked on postaneurysm rupture day 2, and remained increased up to day 6
2. Natriuretic peptides caused sodium and water loss with plasma sodium levels falling between day 3 and 10
3. There were no changes in cardiac indices and slight increases in extravascular lung water indices. There were no changes in intrathoracic blood volume indices.

This study thoroughly discussed relationships between elevated natriuretic peptides and cardiopulmonary parameters after aneurysmal subarachnoid hemorrhage. It had institutional ethics board approval, and clear declaration of funding sources. However, its main

weaknesses included small study sample size, patient selection, and center referral biases.

Article 6: Circulatory characteristics of normovolemia and normotension therapy after subarachnoid hemorrhage, focusing on pulmonary edema

In this prospective cohort study, Sato *et al*. characterized circulatory parameters after severe aneurysmal subarachnoid hemorrhage to reveal mechanisms of pulmonary edema.[11] Over a period of 2 years, 49 adults with aneurysmal subarachnoid hemorrhage were included (average 59 years). Exclusion criteria included patients with brainstem dysfunction and lack of study consent. Clear study protocols were described. Patients were maintained euvolemic. Reference standard tests included chest radiograph and arterial blood gases. Diagnostic tests included pulse contour analysis to measure cardiopulmonary parameters. This study found the following:

1. 7 out of 49 patients experienced neurogenic pulmonary edema
2. Patients with neurogenic pulmonary edema had a lower cardiac function index and lower global ejection fraction. They had higher global end diastolic volume index
3. Even though neurogenic pulmonary edema patients had net negative water balance and low central venous pressures, they had higher extravascular lung water index.

This study thoroughly discussed circulatory changes in aneurysmal subarachnoid hemorrhage patients with neurogenic pulmonary edema. It had institutional ethics board approval, and clear declaration of funding sources. However, its main weaknesses included small study sample size, patient selection, and center selection biases.

Methodological quality of included studies

In summary, all six studies have strong methodologic quality [Table 1]. They had representative patient populations, clear selection criteria and clear descriptions of study designs. Reproducible study protocols with ethics board approval were present. Clinical results were described in sufficient detail and were applicable to aneurysmal subarachnoid hemorrhage patients in clinical practice. There were few study withdrawals. These cases were medical deteriorations and deaths precluding study completion. The main methodologic weakness in all studies included small sample size, patient selection, and center referral biases.

Results gained from these studies are clinically useful and shed light on how ruptured brain aneurysms affect the cardiopulmonary system. Subsequent neuro-cardio-endocrine responses then interact with other body systems, including the renal system, as part of the secondary responses to primary injury.

DISCUSSION

This systematic review gathers the most current methodologically rigorous evidence on known pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage. The following pathophysiologic discussion summaries this current state of knowledge.[1,3-11,13,14]

Rupture of brain aneurysms can lead to overactivity of the sympathetic nervous system. This triggers a sympathetic surge of catecholamine release from the thoracic spinal cord's paravertebral chain. Pathologically, the cardiac ventricle is stunned.[2] This manifests as electrographic changes and troponin elevations.[6,9,10] Troponin changes are more commonly found in those with poor neurological grade, intraventricular hemorrhage, cerebral edema, loss of consciousness at ictus, and multisystem physiological derangements.[9] They are associated with adverse events including left ventricular systolic dysfunction, pulmonary edema, hypotension requiring vasopressors, delayed strokes, and death.[9] Troponin release, however, are not usually as high as levels observed after myocardial infarction secondary to lack of coronary blood flow.[6,9,10] Indeed, cardiac stunning refers to cardiac beta receptor

Table 1: Methodological assessment of articles on brain-body associations in aneurysmal subarachnoid hemorrhage

	Audibert *et al.*[1]	Espiner *et al.*[5]	Inamasu *et al.*[6]	Naidech *et al.*[9]	Nakamura *et al.*[10]	Sato *et al.*[11]
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort
Representativeness of cohort	Yes	Yes	Yes	Yes	Yes	Yes
Selection criteria	Clear	Clear	Clear	Clear	Clear	Clear
Reference standard used?	Yes	Yes	Yes	Yes	Yes	Yes
Index test reproducible?	Yes	Yes	Yes	Yes	Yes	Yes
Clinical data applicable to clinical practice?	Yes	Yes	Yes	Yes	Yes	Yes
Noninterpretable test results reported?	Yes	Yes	Yes	Yes	Yes	Yes
Withdrawals explained?	Yes	Yes	Yes	No study withdrawals	Yes	No study withdrawals
Measure clinically useful?	Yes	Yes	Yes	Yes	Yes	Yes

hyperactivation and hypercontraction where contraction band necrosis can result. An extreme case of this, is the observation of stunned apical and midventricular segments in takotsubo-like cardiomyopathy.[6] Electrocardiographic, troponin, and echocardiographic evidence correlate with blood measurement of brain natriuretic peptide, a protein released from the cardiac ventricle with peak values on postrupture day 1.[1,5,10,11] The brain site of brain natriuretic peptide production does not seem to be as affected as cerebrospinal fluid levels of brain natriuretic peptide are not elevated.[1,5,10,11] Further physiologic evidence from pulse contour analysis point to a global decrease in cardiac ejection fraction, with a subsequent increase in extravascular lung water index by postrupture day 3.[10,11] This is consistent with increased catecholamines in peripheral arterioles which can increase pulmonary venous pressures and enhance pulmonary vascular permeability.[1,3-11,13,14] The combination of increase pulmonary vascular permeability, increased pulmonary vascular pressure, decreased cardiac contractility, and increased volume from resuscitation can lead to hydrostatic pulmonary edema where hydrostatic pressures favoring edema formation overwhelms the opposing oncotic pressures. As a result of the apparent increased preload, the cardiac atrium is stretched.[1,5,10,11] Plasma atrial natriuretic peptide levels peak at postrupture day 2 after aneurysmal rupture. Cerebrospinal fluid levels of atrial natriuretic peptides remain normal suggesting that the primary source of atrial natriuretic peptide release is the cardiac atrium and not the brain.

Together, atrial and brain natriuretic peptides then act on renal tubules triggering sodium and volume loss. Without appropriate resuscitation, plasma sodium levels can fall drastically by postrupture day 4–6.[10,11] This drop can be attenuated with preemptive judicious volume and salt replacement. With this treatment, the incidence of severe clinical vasospasm can be lowered.[1] Natriuretic and diuretic states in aneurysmal subarachnoid hemorrhage often herald the onset of clinical vasospasm. Between days 4 and 6, the renin-angiotensin-aldosterone system is activated.[1,3-11,13,14] Figure 3 shows pathophysiologic mechanisms of brain-body associations after aneurysmal subarachnoid hemorrhage, as well as interrelationships, between the neuro-cardio-endocrine systems and the renin-angiotensin-aldosterone system. This system is activated in a delayed manner as a compensatory mechanism for prior sodium and water loss. Waiting for this mechanism alone to compensate for sodium and water balance in the aneurysmal subarachnoid hemorrhage patient will have severe negative consequences because the onset of vasospasm can lead to delayed strokes and further secondary neurological damage.

Clinical implications

This systematic review elucidates mechanisms of how ruptured brain aneurysms affect neuroendocrine, heart,

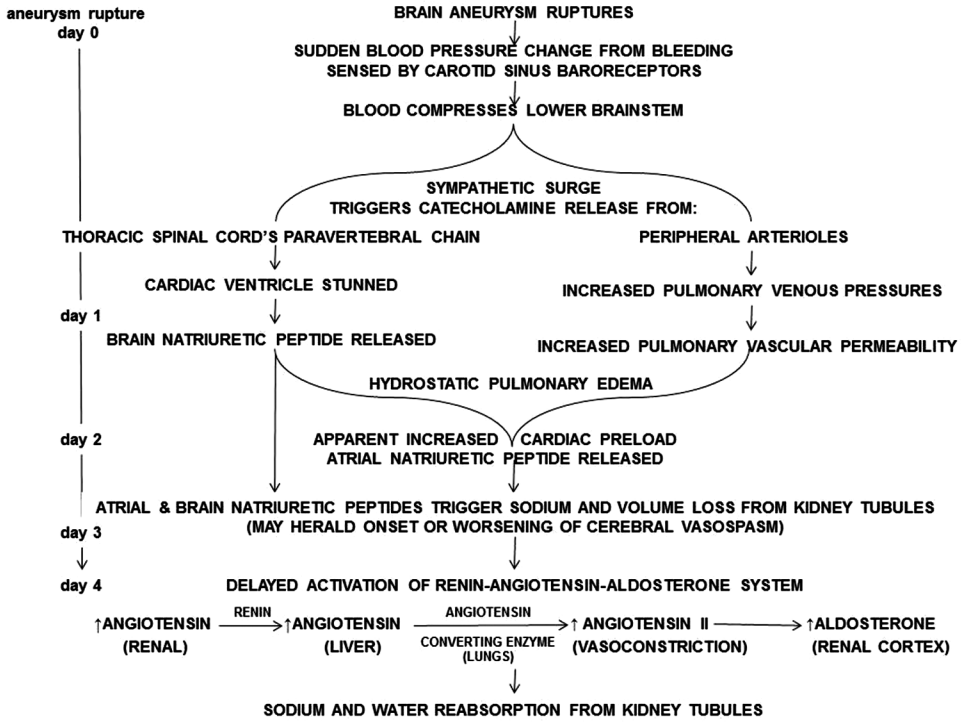


Figure 3: Pathophysiologic mechanisms of brain-body associations after aneurysmal subarachnoid hemorrhage and delayed activation of the renin-angiotensin-aldosterone system

lung, as well as fluid, and electrolyte balance in the affected patients. Recognition of pathophysiologic mechanisms of brain-body associations is essential in preventing complications after treatment of ruptured brain aneurysms. The clinician should be vigilant about:

1. Maintenance of sodium and water balance,
2. Potential negative impact of agents which interfere with the renin-angiotensin-aldosterone system (including corticosteroids and angiotensin-converting enzyme inhibitors),
3. Ventilatory support to overcome pulmonary edema, and
4. Inotropic and vasopressor support for the stunned myocardium.

Limitations

This systematic review included studies with small sample sizes. Highly selected patient populations were included, with short-term follow-up. Differing diagnostic tests were used to clarify pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms, with no standardization of diagnostic tests between investigating centers. Because of these limitations, individual patient variability in physiologic responses may not be adequately captured.

Patients with underlying comorbidities such as gastrointestinal diseases were not included to clarify the effects of other comorbidities on pathophysiologic mechanisms of brain-body associations in aneurysmal subarachnoid hemorrhage patients. In addition, there is scarce epidemiologic evidence to demonstrate the clinical associations between ruptured brain aneurysms and the gastrointestinal, immune and hematologic systems.

CONCLUSION

This systematic review synthesizes the most current evidence of underlying mechanisms of brain related associations with body systems in aneurysmal subarachnoid hemorrhage. However, literature is still lacking on some key mechanisms including the reasons for early-onset cerebral edema in the aneurysmal subarachnoid hemorrhage patient, which is an important cause of early hospital associated mortality. In addition, the mechanisms of late hospital associated mortality are not well described in large epidemiologic aneurysmal subarachnoid hemorrhage populations. There is also insufficient epidemiologic evidence of associations between the brain-gastrointestinal and brain-immune systems.

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