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Review
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The neurocardiac axis in traumatic brain injury – an endless pathophysiological hot spot

Cristian **Cobilinschi** [1, 2] *, Radu **Tincu** [3, 4], Claudia **Cobilinschi** [5, 6], Ioana **Grintescu** [1, 2]

[1] Department of Anaesthesiology and Intensive Care I, Bucharest Clinical Emergency Hospital, Bucharest, Romania
[2] Department of Anaesthesiology and Intensive Care II, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3] Department of Anaesthesiology and Intensive Care II – Toxicology, Bucharest Clinical Emergency Hospital, Bucharest, Romania
[4] Department of Toxicology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[5] Department of Internal Medicine, Sf Maria Clinical Hospital, Bucharest, Romania
[6] Department of Internal Medicine and Rheumatology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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Abstract

Traumatic brain injury (TBI) continues to be one of the leading causes of morbidity and mortality worldwide. Depending on the type of traumatic mechanical forces that act on the skull, primary polymorphic injuries may occur due to the direct impact. Secondary injuries are usually rapidly induced in the acute phase after the initial hit and are represented by neuroinflammation, cerebral edema, or ischemia. As in every acute stress condition, sympathetic activation is the primary and central pathophysiological alteration after TBI, being responsible for the more significant part of the systemic organ damage, systemic inflammation, and finally for the poor outcome. Massive catecholamine release translates into massive peripheral vasoconstriction and raised systemic vascular resistance, an entity frequently recognized as "neurogenic hypertension". Catecholamine cardiotoxicity may induce stress cardiomyopathy, characterized by myocytolysis or contraction band necrosis, induced by accelerated myocardial necrosis in a hypercontracted state. If stress cardiomyopathy was reported to occur simultaneously with a stressful event, like TBI, another similar entity named neurogenic stunned myocardium was described to arise secondary to the primary neurologic pathology. A reversible microcirculatory dysfunction has also been identified. Considering the rationale of beta-blocker use in patients with concomitant TBI and stress cardiomyopathy, further homogenous trials are needed to establish benefits and safety.

Keywords: trauma brain injury, intracranial hypertension, heart-brain axis, neurogenic hypertension, catecholamine, stress cardiomyopathy, Takotsubo, neurogenic stunned myocardium.

* Correspondence to: Cristian COBILINSCHI,
Department of Anaesthesiology and Intensive Care I,
Bucharest Clinical Emergency Hospital, Bucharest, Romania.
Phone: 0040765018776; E-mail: cob_rodion@yahoo.com

Introduction

Traumatic brain injury (TBI) continues to be one of the leading causes of mortality and disability in young adults [1–3]. Through high healthcare costs, this so-called "silent epidemic" represents a burden for every national healthcare system worldwide [1, 2]. The principal causes of TBI are represented by falls, road injuries, and sports accidents [2, 4]. The incidence of this pathological entity is age-related and has three peaks: first during early childhood, second in early adulthood and the last after the age of 75. Thus, adequate management for these patients is the aim of many different medical specialties [4].

TBI has been classified as primary and secondary injuries for more than 20 years, although this depiction has proved to be rather synthetic as both processes are intimately tied [5]. Primary injury caused by initial mechanical forces (acceleration and deceleration, penetrating or blast trauma) may cause focal contusions, hemorrhages, or diffuse axonal injuries, often not easily identified during initial investigations [6]. Secondary injuries supervene the initial lesions and are usually related to ischemic origins, such as hypo-/hypertension, hypo-/hyperthermia, acidosis, hypo-/hyperglycaemia, or anemia [7]. Considering that primary injuries are associated with irreversible changes, secondary injuries are the main therapeutic goals for TBI patients [7].

As in every acute stress condition, sympathetic activation is the primary and central pathophysiological alteration after TBI, being responsible for the larger part of the systemic organ damage, systemic inflammation, and finally for the poor outcome [8]. The current article review describes the brain-heart interaction and its implication on the cardiovascular system in patients with TBI.

Heart-brain axis - physiological aspects

The link between the heart and the brain has already been described several decades ago, along with the Cushing reflex (bradycardia and hypertension) [9]. Since then, an extensive brain-heart network, called the central autonomic network (CAN), was described [10]. CAN links cortices structures, like the medial prefrontal cortex, the insula cortex, subcortical structures – amygdala, hypothalamus, and brain stem areas like the periaqueductal grey matter and the pons parabrachial Kölliker-Fuse region [9, 10].

Experimental studies have revealed that the insular cortex has a central role in modulating the neuro-cardiac axis through viscerosensory and visceromotor functions [10]. According to "the laterality hypothesis", the right insula is associated with sympathetic regulation of the cardiovascular activity, and lesions on the left insula are implicated in parasympathetic modulation, converting to a predominance of cardiac sympathetic tone [9, 11]. Clinical data revealed that patients with an ischemic stroke affecting the left insular cortex encounter sympathetic overstimulation while ischemic stroke on the right insular cortex may cause neurogenic stand myocardium [12]. However, data based on humans and neuroimaging studies have not confirmed the exact location of cardiac motor regions, and the lateralization theory remains questionable [13]. Chouchou *et al.* demonstrated that sympathetic and parasympathetic systems are equally represented in both right and left insular regions, with a slight asymmetry between their subregions [13]. After leaving the central nervous system, sympathetic efferent fibers synapse in the stellate ganglia, and postganglionic fibers distribute predominantly around the sinus node and coronary sinus. Preganglionic parasympathetic fibers synapse within the intrinsic cardiac ganglia and spread afterward to the atria and ventriculi, including the sinus and atrioventricular node [14]. The sympathetic effects are mediated through beta-1, and postganglionic parasympathetic stimulate M2 muscarinic receptors [9].

From TBI to neurogenic hypertension

Depending on the type of traumatic mechanical forces that act on the skull, primary polymorphic injuries may occur due to the direct impact [6]. The primary insult causes a coup characterized by necrotic neurons and glial cells and shearing of the axons and vessels, precipitating intracerebral, epidural, and subdural hemorrhages [15, 16]. Supplementary lesions are described in the opposite areas or surrounding the primary injury due to the rebound of the brain tissue (contrecoup) [15, 17].

Secondary injuries are usually rapidly induced in the acute phase after the initial hit [17]. Increased levels of glutamate and aspartate may cause hyperactivation of N-methyl-D-aspartate (NMDA) and alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors leading to neurons depolarization - an excitotoxicity effect [15]. Exacerbated Ca^{2+} ions release, induced by glutamate, produces mitochondrial dysfunction, increases oxidative stress and finally promotes neuronal cells death [16, 18]. Furthermore, high levels of glutamate favors "hyperglycolysis", defined by rapid glucose depletion and lactate accumulation due to mitochondrial dysfunction [6, 18, 19]. All these cellular alterations associated with electrolyte imbalance and osmotic gradients' variations ultimately lead to cytotoxic edema [4, 6, 20]. Although these cellular changes are referred to as cytotoxic edema, studies revealed that there is only an intracellular fluid accumulation caused by

oncotic cell swelling [21]. The second type of edema described after TBI – vasogenic edema – is caused by endothelial cell sheet disruption through which electrolytes, proteins, and water shift from the intravascular space and accumulate extracellularly [6, 16, 20]. This type of edema associated with blood-brain-barrier (BBB) breakdown proved to be more detrimental, causing extracellular edema and brain swelling [21].

According to the Kellie-Monroe doctrine, an increase in brain parenchyma imposes the decrease of all the remaining components (cerebrospinal fluid and cerebral blood flow reduction) [21–23]. Although the initial intracranial volume increase may be compensated, these mechanisms are rapidly exhausted, and intracranial pressure develops [22, 23]. Increased intracranial pressure (ICP) above the level of mean arterial pressure (MAP) will affect cerebral perfusion pressure (CPP), resulting in autoregulation mechanism failure with a rightward shift of the regulation curve [4, 8, 16, 22]. After compromising the mechanism of preserving a continuous cerebral blood flow, an alternation of hypoperfusion and hyperemia may occur ("luxury perfusion") [8, 24, 25]. Nevertheless, increased ICP was already recognized as the main contributor to the exacerbated sympathetic outflow in patients with TBI [6, 26].

Both primary and secondary injuries are associated with damage-associated molecular patterns (DAMPS) production, which in turn activate a local immune response, including increased cytokine release (tumor-necrosis-factor-alfa – (TNF-alfa), interleukin-6 (IL-6), interleukin 1-beta (IL-1 beta) [15, 20]. This early cytokine release is associated with further BBB injury, maintaining a continuous vicious cycle [15]. Increased IL-1 beta contributes to early sympathetic nervous system (SNS) activation and, in return, increased levels of catecholamines impact cytokine release from leukocytes through adrenergic receptors' modulation [27].

Neuroendocrine pathways activation during TBI has already been proven to be in a tight bidirectional relationship with the increased neuroinflammatory response, released cytokines, like TNF-alfa or IL-6 being potent activators of the hypothalamic-pituitary-adrenal axis [28]. The initial phase after trauma is characterized by the increased sympathoadrenal response, secondary to hypothalamic activation, increased catecholamines, corticotropin, cortisol, thyroid hormones, and growth hormone release [29, 30]. Catecholamine exacerbated release secondary to hypothalamic stimulation was also demonstrated through experimental studies [31]. Although this initial phase may be typical for every stressful situation, cortisol effects in patients with TBI are altered and are influenced by various factors like the affected brain region, damaged cell types, or exogenous glucocorticoid administration [28]. However, Kusmenkov *et al.* demonstrated that cortisol levels decreased rapidly, and after the first 24 hours, patients with TBI may experience a lower total and free cortisol concentration, exposed to inadequate stress response [32].

Most of the pathophysiological alterations associated with TBI have a merged effect resulting in a complex cascade of catecholamine release [27]. As in any "fight or flight" reaction, SNS replies through massive adrenaline and noradrenaline release into the periphery in order to restore homeostasis [27, 33]. Although sympathetic nervous system activation and increased catecholamine release are to be expected as an essential survival response, excessive and prolonged hyperadrenergic response proved to be associated with a worse outcome, characterized by severe brain injuries, multisystemic dysfunction, and increased mortality [34–36]. In a prospective, observational study, Rizoli *et al.* reported that the extensive catecholamine release is an independent prognostic factor and that the catecholamine peak levels are proportional with the brain injury severity [34].

Clinically, massive catecholamine release translates into massive peripheral vasoconstriction and raised systemic vascular resistance, an entity frequently named "neurogenic hypertension" [8].

From TBI to cardiac dysfunction - common pathophysiology for many different entities

Association between brain injuries and myocardial dysfunction has already been signaled from the late '60s [37]. Since then, various brain injury-related cardiac pathologies have been described, including Takotsubo cardiomyopathy, transient systolic dysfunction, neurogenic stunned myocardium, or reverse acute heart failure [38]. Regardless of the clinical pattern, in most of the cases, catecholamine-induced pathological features were highlighted [39]. Interestingly, experimental studies revealed that the increased levels of catecholamines from the myocardial interstitium are not necessarily correlated with increased catecholamine plasma levels [40].

Histopathological changes typically caused by catecholamine cardiotoxicity are represented by myocytolysis or contraction band necrosis induced by accelerated myocardial necrosis in a hypercontracted state [41, 42]. These specific myocardial transformations are explained through extensive Ca^{2+} ions influx secondary to beta-1 receptor overstimulation, induced by catecholamines in the context of lower oxygen levels, usually illustrated on the electrocardiogram through peaked T waves [39, 40, 43]. Nevertheless, another particular histopathological feature is represented by a rich interstitial mononuclear infiltrate [42].

Considering the distribution of beta-adrenoreceptors and sympathetic innervation in the left apical ventricle (higher receptor density and lower sympathetic nerve density), an apical-basal gradient

was depicted [39, 42]. This gradient is thought to be responsible for the apical left ventricle kinetic anomalies (reversible akinesia or hypokinesia of the apex), usually described in Takotsubo syndrome or stress cardiomyopathy [38, 42]. In other words, it was reported that the cardiac apex might have a higher sensibility to increased levels of catecholamines, which may cause a reduced coronary blood flow as well as a negative inotropic effect in this area [44]. Negative inotropic effects are considered to be induced by a "molecular switch" of the beta-2 adrenergic receptors through uncoupling from the Gs protein pathway and coupling to Gi protein [44]. Heubach *et al.* revealed that only adrenaline and not noradrenaline are able to couple beta-2 adrenergic receptors, which may be a protective mechanism against Gs protein overstimulation in the presence of high levels of noradrenaline [45].

Growing reports about "atypical" or "inverted" Takotsubo (akinesia of the basal left ventricle and hyperkinesia of the apex) were identified, emphasizing that the incidence of this particular cardiomyopathy is higher than initially thought [42, 46, 47]. Since available experimental data is still incomplete, the pathophysiology mechanisms of this inverted Takotsubo cardiomyopathy are still uncertain [46]. However, interindividual variability of the distribution of the adrenergic receptors is highly suspected [47].

If stress cardiomyopathy was reported to coincide with a stressful event like TBI, another similar entity, named neurogenic stunned myocardium (NSM), was described to arise secondary to the primary neurologic pathology [39]. Considering that both entities have common pathophysiological and clinical features, it is considered that NSM is only a different presentation of the same pathology [31, 39, 48]. The main difference between Takotsubo cardiomyopathy and NSM is represented by the fact that apical dysmotility is common in Takotsubo cardiomyopathy while basal akinesia/hypokinesia is frequent in NSM [31, 39].

It was also reported that a reversible microcirculatory dysfunction might also be described in patients with stress cardiomyopathy [31, 49]. Galiuto *et al.* reported that all patients with Takotsubo syndrome included in their observational study presented a perfusion defect due to a coronary microvascular dysfunction, which was transitorily ameliorated after adenosine administration and completely one month after the acute injury [49].

TBI-related cardiac dysfunction – therapeutic aspects

Considering that the main pathophysiological process incriminated to be responsible for stress cardiomyopathy is represented by exacerbated catecholamine release, the expected therapeutic target may be a counteraction against sympathetic storm [42, 43]. In this regard, beta-blocker administration seems to be the treatment with the best potential benefit [26, 31, 50].

Taking into consideration that besides beta-1 adrenoreceptors overstimulation, a negative inotropic effect mediated by beta-2 adrenoreceptor may occur, an unselective beta-receptor antagonist should be considered [50]. The use of beta-blockers with adequate pharmacokinetics properties proved to have simultaneously beneficial effects on the myocardium and the brain [50–52]. The experimental study conducted by Armstead *et al.*, which included thirty pigs, revealed that propranolol administration was associated with lower cerebral inflammation levels but also with the prevention of hypotensive dilatation impairment [52]. Murry *et al.* indicated that early use of propranolol in patients with TBI was associated with decreased hospital length of stay without registering an increase in bradycardic and hypotensive events [51]. However, Akashi *et al.* singled out that the use of combined alfa and beta-blocker may be a better choice, considering that supplementary alfa blocking may prevent platelet activation and thrombosis induced by adrenaline through alfa-2 adrenoreceptors [53]. The selection of combined alfa and beta-blocker was reported to be rather unsafe, considering the high risk of cerebral blood flow endanger secondary to induced hypotension [50].

Conclusion

Traumatic brain injury associated with cardiac dysfunction is a frequent entity that is often misdiagnosed. The principal mechanism of cardiac dysfunction is represented by catecholamine overstimulation as a result of pathological changes induced by TBI. Although a variety of entities were described, stress cardiomyopathy is characterized by transient myocardial dyskinesia and is usually associated with a favorable prognostic. Considering the rationale of beta-blocker use in patients with concomitant TBI and stress cardiomyopathy, further homogenous trials are needed in order to establish the benefits and safety of this treatment.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

References

1. M. C. Dewan, A. Rattani, S. Gupta, R. E. Baticulon, Y. C. Hung, M. Punchak, A. Agrawal, A. O. Adeleye, M. G. Shrime, A. M. Rubiano, J. V. Rosenfeld, and K. B. Park, "Estimating the global incidence of traumatic brain injury", J. Neurosurg., vol. 130, no. 4, pp. 1080–1097, 2019, doi: 10.3171/2017.10.JNS17352.
2. S. L. James, M. S. Bannick, W. C. Montjoy-Venning, L. R. Lucchesi, L. Dandona, R. Dandona, C. Hawley, S. I. Hay, M. Jakovljevic, I. Khalil, K. J. Krohn, A. H. Mokdad, M. Naghavi, E. Nichols, R. C. Reiner, M. Smith, V. L. Feigin, T. Vos, C. J. L. Murray, *et al.*, "Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016", Lancet Neurol., vol. 18, no. 1, pp. 56–87, 2019, doi: 10.1016/S1474-4422(18)30415-0.
3. J. A. Haagsma, N. Graetz, I. Bolliger, M. Naghavi, H. Higashi, E. C. Mullany, S. F. Abera, J. P. Abraham, K. Adofo, U. Alsharif, E. A. Ameh, W. Ammar, C. A. T. Antonio, L. H. Barrero, T. Bekele, D. Bose, A. Brazinova, F. Catalá-López, L. Dandona, *et al.*, "The global burden of injury: Incidence, mortality, disability-adjusted life years and time trends from the global burden of disease study 2013", Inj. Prev., vol. 22, no. 1, pp. 3–18, 2016, doi: 10.1136/injuryprev-2015-041616.
4. K. Hackenberg and A. Unterberg, "Schädel-Hirn-Trauma", Nervenarzt, vol. 87, no. 2, pp. 203–216, 2016, doi: 10.1007/s00115-015-0051-3.
5. M. Greve and B. Zink, "Pathophysiology of Traumatic Brain Injury", Mt. Sinai J. Med., vol. 76, pp. 97–104, 2009, doi: 10.1002/MSJ.
6. E. P. Raith, F. Fiorini, and U. Reddy, "Critical care management of adult traumatic brain injury", Anaesth. Intensive Care Med., vol. 21, no. 6, pp. 285–292, 2020, doi: 10.1016/j.mpaic.2020.03.012.
7. S. H. Haddad and Y. M. Arabi, "Critical care management of severe traumatic brain injury in adults", Scand. J. Trauma. Resusc. Emerg. Med., vol. 20, no. 1, p. 12, 2012, doi: 10.1186/1757-7241-20-12.
8. K. Kinoshita, "Traumatic brain injury: Pathophysiology for neurocritical care", J. Intensive Care, vol. 4, no. 1, pp. 1–10, 2016, doi: 10.1186/s40560-016-0138-3.
9. P. Tahsili-Fahadan and R. G. Geocadin, "Heart-Brain Axis: Effects of Neurologic Injury on Cardiovascular Function", Circ. Res., vol. 120, no. 3, pp. 559–572, 2017, doi: 10.1161/CIRCRESAHA.116.308446.
10. A. Silvani, G. Calandra-buonaura, R. A. L. Dampney, P. Cortelli, and P. Cortelli, "Brain – heart interactions: physiology and clinical implications", R. Soc. Publ., vol. A, no. 374, pp. 1–22, 2016.
11. S. M. Oppenheimer, G. Kedem, and W. M. Martin, "Left-insular cortex lesions perturb cardiac autonomic tone in humans", Clin. Auton. Res., vol. 6, no. 3, pp. 131–140, 1996, doi: 10.1007/BF02281899.
12. A. Prasad Hrishi, K. Ruby Lionel, and U. Prathapadas, "Head Rules Over the Heart: Cardiac Manifestations of Cerebral Disorders", Indian J. Crit. care Med. peer-reviewed, Off. Publ. Indian Soc. Crit. Care Med., vol. 23, no. 7, pp. 329–335, Jul. 2019, doi: 10.5005/jp-journals-10071-23208.
13. F. Chouchou, F. Mauguière, O. Vallayer, H. Catenoix, J. Isnard, A. Montavont, J. Jung, V. Pichot, S. Rheims, and L. Mazzola, "How the insula speaks to the heart: Cardiac responses to insular stimulation in humans", Hum. Brain Mapp., vol. 40, no. 9, pp. 2611–2622, 2019, doi: 10.1002/hbm.24548.
14. W. A. Huang, N. G. Boyle, and M. Vaseghi, "Cardiac Innervation and the Autonomic Nervous System in Sudden Cardiac Death", Card. Electrophysiol. Clin., vol. 9, no. 4, pp. 665–679, 2017, doi: 10.1016/j.ccep.2017.08.002.
15. S. Y. Ng and A. Y. W. Lee, "Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets", Front. Cell. Neurosci., vol. 13, no. November, pp. 1–23, 2019, doi: 10.3389/fncel.2019.00528.
16. P. Kaur and S. Sharma, "Recent Advances in Pathophysiology of Traumatic Brain Injury", Curr. Neuropharmacol., vol. 16, no. 8, pp. 1224–1238, 2017, doi: 10.2174/1570159x15666170613083606.
17. J. D. Medaglia, "Functional neuroimaging in traumatic brain injury: From nodes to networks", Front. Neurol., vol. 8, no. AUG, pp. 1–18, 2017, doi: 10.3389/fneur.2017.00407.
18. A. Capizzi, J. Woo, and M. Verduzco-Gutierrez, "Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management", Med. Clin. North Am., vol. 104, no. 2, pp. 213–238, 2020, doi: 10.1016/j.mcna.2019.11.001.
19. G. Cassol, D. B. Godinho, V. N. de Zorzi, J. B. Farinha, I. D. Della-Pace, M. de Carvalho Gonçalves, M. S. Oliveira, A. F. Furian, M. R. Fighera, and L. F. F. Royes, "Potential therapeutic implications of ergogenic compounds on pathophysiology induced by traumatic brain injury: A narrative review", Life Sci., vol. 233, no. July, p. 116684, 2019, doi: 10.1016/j.lfs.2019.116684.
20. R. M. Jha, P. M. Kochanek, and J. M. Simard, "Pathophysiology and treatment of cerebral edema in traumatic brain injury", Neuropharmacology, vol. 145, no. March 2018, pp. 230–246, 2019, doi: 10.1016/j.neuropharm.2018.08.004.
21. J. A. Stokum, V. Gerzanich, and J. M. Simard, "Molecular pathophysiology of cerebral edema", J. Cereb. Blood Flow Metab., vol. 36, no. 3, pp. 513–538, 2016, doi: 10.1177/0271678X15617172.
22. R. M. Jha and P. M. Kochanek, "A Precision Medicine Approach to Cerebral Edema and Intracranial Hypertension after Severe Traumatic Brain Injury: Quo Vadis?", Curr. Neurol. Neurosci. Rep., vol. 18, no. 12, p. 105, Nov. 2018, doi: 10.1007/s11910-018-0912-9.
23. V. Wykes and R. Vindlacheruvu, "Intracranial pressure, cerebral blood flow and brain oedema", Surg. (United Kingdom), vol. 33, no. 8, pp. 355–362, 2015, doi: 10.1016/j.mpsur.2015.06.001.
24. A. Schubert, "Cardiovascular therapy of neurosurgical patients", Best Pract. Res. Clin. Anaesthesiol.,

vol. 21, no. 4, pp. 483–496, 2007, doi: 10.1016/j.bpa.2007.06.003.
25. N. A. Lassen, "The luxury perfusion syndrome", Scand. J. Clin. Lab. Invest., vol. 21, no. s102, pp. 10–12, 1968, doi: 10.3109/00365516809169022.
26. H. E. Hinson and K. N. Sheth, "Manifestations of the hyperadrenergic state after acute brain injury", Curr. Opin. Crit. Care, vol. 18, no. 2, pp. 139–145, 2012, doi: 10.1097/MCC.0b013e3283513290.
27. A. P. Di Battista, S. G. Rhind, M. G. Hutchison, S. Hassan, M. Y. Shiu, K. Inaba, J. Topolovec-Vranic, A. C. Neto, S. B. Rizoli, and A. J. Baker, "Inflammatory cytokine and chemokine profiles are associated with patient outcome and the hyperadrenergic state following acute brain injury", J. Neuroinflammation, vol. 13, no. 1, pp. 1–14, 2016, doi: 10.1186/s12974-016-0500-3.
28. M. Santarsieri, R. G. Kumar, P. M. Kochanek, S. Berga, and A. K. Wagner, "Variable neuroendocrine-immune dysfunction in individuals with unfavorable outcome after severe traumatic brain injury", Brain. Behav. Immun., vol. 45, pp. 15–27, 2015, doi: 10.1016/j.bbi.2014.09.003.
29. J. P. Desborough, "The stress response to trauma and surgery", Br. J. Anaesth., vol. 85, no. 1, pp. 109–117, 2000, doi: 10.1093/bja/85.1.109.
30. D. Tomescu, C. Cobilinschi, A. Baetu, A. Totan, P. T. Neagu, C. C. Diaconu, I. F. Tincu, A. P. Stoian, O. G. Bratu, and R. A. Macovei, "Effects of acute organophosphate poisoning on glycemic profile in weanling rats", Rev. Chim., vol. 69, no. 12, 2018.
31. B. B. Kenigsberg, C. F. Barnett, J. C. Mai, and J. J. Chang, "Neurogenic Stunned Myocardium in Severe Neurological Injury", Curr. Neurol. Neurosci. Rep., vol. 19, no. 11, 2019, doi: 10.1007/s11910-019-0999-7.
32. T. Kusmenkov, M. Braunstein, H. J. Schneider, M. Bidlingmaier, W. C. Prall, W. Flatz, W. Boecker, and V. Bogner, "Initial free cortisol dynamics following blunt multiple trauma and traumatic brain injury: A clinical study", J. Int. Med. Res., vol. 47, no. 3, pp. 1185–1194, 2019, doi: 10.1177/0300060518819603.
33. C. H. Gibbons, Basics of autonomic nervous system function, 1st ed., vol. 160. Elsevier B.V., 2019. doi: 10.1016/B978-0-444-64032-1.00027-8.
34. S. B. Rizoli, B. N. R. Jaja, A. P. Di Battista, S. G. Rhind, A. C. Neto, L. da Costa, K. Inaba, L. T. da Luz, B. Nascimento, A. Perez, A. J. Baker, and A. L. de Oliveira Manoel, "Catecholamines as outcome markers in isolated traumatic brain injury: The COMA-TBI study", Crit. Care, vol. 21, no. 1, pp. 1–10, 2017, doi: 10.1186/s13054-017-1620-6.
35. A. P. Di Battista, S. B. Rizoli, B. Lejnieks, A. Min, M. Y. Shiu, H. T. Peng, A. J. Baker, M. G. Hutchison, N. Churchill, K. Inaba, B. B. Nascimento, A. L. De Oliveira Manoel, A. Beckett, and S. G. Rhind, "Sympathoadrenal Activation is Associated with Acute Traumatic Coagulopathy and Endotheliopathy in Isolated Brain Injury", Shock, vol. 46, no. 3S, pp. 96–103, 2016, doi: 10.1097/SHK.0000000000000642.
36. S. Andrei, S. Isac, M. Carstea, C. Martac, L. Mihalcea, C. Buzatu, D. Ionescu, D. Georgescu, and G. Droc, "Isolated liver trauma: A clinical perspective in a non-emergency center for liver surgery", Exp. Ther. Med., vol. 23, no. 1, pp. 1–5, 2021, doi: 10.3892/etm.2021.10961.
37. R. C. R. Connor, "Myocardial damage secondary to brain lesions", Am. Heart J., vol. 78, no. 2, pp. 145–148, 1969.
38. J. Finsterer and K. Wahbi, "CNS disease triggering Takotsubo stress cardiomyopathy", Int. J. Cardiol., vol. 177, no. 2, pp. 322–329, 2014, doi: 10.1016/j.ijcard.2014.08.101.
39. J. G. Ripoll, J. L. Blackshear, and J. L. Díaz-Gómez, "Acute Cardiac Complications in Critical Brain Disease", Neurosurg. Clin. N. Am., vol. 29, no. 2, pp. 281–297, 2018, doi: 10.1016/j.nec.2017.11.007.
40. H. Nguyen and J. G. Zaroff, "Neurogenic stunned myocardium", Curr. Neurol. Neurosci. Rep., vol. 9, no. 6, pp. 486–491, 2009, doi: 10.1007/s11910-009-0071-0.
41. M. A. Samuels, "The brain-heart connection", Circulation, vol. 116, no. 1, pp. 77–84, 2007, doi: 10.1161/CIRCULATIONAHA.106.678995.
42. S. Mrozek, J. Gobin, J. M. Constantin, O. Fourcade, and T. Geeraerts, "Crosstalk between brain, lung and heart in critical care", Anaesth. Crit. Care Pain Med., vol. 39, no. 4, pp. 519–530, 2020, doi: 10.1016/j.accpm.2020.06.016.
43. V. Krishnamoorthy, G. Burkhard Mackensen, E. F. Gibbons, and M. S. Vavilala, "Cardiac dysfunction after neurologic injury what do we know and where are we going?", Chest, vol. 149, no. 5, pp. 1325–1331, 2016, doi: 10.1016/j.chest.2015.12.014.
44. J. R. Ghadri, I. S. Wittstein, A. Prasad, S. Sharkey, K. Dote, Y. J. Akashi, V. L. Cammann, F. Crea, L. Galiuto, W. Desmet, T. Yoshida, R. Manfredini, I. Eitel, M. Kosuge, H. M. Nef, A. Deshmukh, A. Lerman, E. Bossone, R. Citro, *et al.*, "International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology", Eur. Heart J., vol. 39, no. 22, pp. 2032–2046, 2018, doi: 10.1093/eurheartj/ehy076.
45. J. F. Heubach, U. Ravens, and A. J. Kaumann, "Epinephrine activates both Gs and Gi pathways, but norepinephrine activates only the Gs pathway through human β2-adrenoceptors overexpressed in mouse heart", Mol. Pharmacol., vol. 65, no. 5, pp. 1313–1322, 2004, doi: 10.1124/mol.65.5.1313.
46. S. Kim, A. Yu, L. A. Filippone, D. M. Kolansky, and A. Raina, "Inverted-Takotsubo pattern cardiomyopathy secondary to pheochromocytoma: A clinical case and literature review", Clin. Cardiol., vol. 33, no. 4, pp. 200–205, 2010, doi: 10.1002/clc.20680.
47. M. Riera, J. A. Llompart-Pou, A. Carrillo, and C. Blanco, "Head Injury and Inverted Takotsubo Cardiomyopathy", J. Trauma, vol. 68, no. 1, pp. E13–E15, 2010, doi: 10.1097/TA.0b013e3181469d5b.
48. L. Gherasim, "Takotsubo Syndrome versus Neurogenic Stunned Myocardium", Maedica (Buchar)., vol. 15, no. 3, pp. 288–296, 2020, doi: 10.26574/maedica.2020.15.3.288.
49. L. Galiuto, A. R. De Caterina, A. Porfidia, L. Paraggio, S. Barchetta, G. Locorotondo, A. G. Rebuzzi, and F.

Crea, "Reversible coronary microvascular dysfunction: A common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome", Eur. Heart J., vol. 31, no. 11, pp. 1319–1327, 2010, doi: 10.1093/eurheartj/ehq039.

50. M. van der Jagt and D. R. Miranda, "Beta-blockers in intensive care medicine: Potential benefit in acute brain injury and acute respiratory distress syndrome", Recent Pat. Cardiovasc. Drug Discov., vol. 7, no. 2, pp. 141–151, 2012, doi: 10.2174/157489012801227274.
51. J. S. Murry, D. M. Hoang, G. Barmparas, M. Y. Harada, M. Bukur, M. B. Bloom, K. Inaba, D. R. Margulies, A. Salim, and E. J. Ley, "Prospective evaluation of early propranolol after traumatic brain injury", J. Surg. Res., vol. 200, no. 1, pp. 221–226, 2015, doi: 10.1016/j.jss.2015.06.045.
52. W. M. Armstead and M. S. Vavilala, "Propranolol protects cerebral autoregulation and reduces hippocampal neuronal cell death through inhibition of interleukin-6 upregulation after traumatic brain injury in pigs", Br. J. Anaesth., vol. 123, no. 5, pp. 610–617, 2019, doi: 10.1016/j.bja.2019.07.017.
53. Y. J. Akashi, H. M. Nef, and A. R. Lyon, "Epidemiology and pathophysiology of Takotsubo syndrome", Nat. Rev. Cardiol, pp. 1–38, 2015, [Online]. Available: www.nature.com/nrcardio