Case Report

SAGE Open Medical Case Reports

Stroke-heart syndrome: A case report and mini literature review

SAGE Open Medical Case Reports
Volume 11: 1–6

DOI: 10.1177/2050313X231183869
journals.sagepub.com/home/sco
Sage

Katrin Henke[1], Aikaterini Galimanis[2], Isaac Blaser[3] and Mairi Ziaka[1]

Abstract

Despite the fact that cardiac troponin (cTn) elevation is commonly seen in the acute phase of ischemic stroke, investigating its etiology represents a challenge for healthcare practitioners. Therefore, we describe the case of an 86-year-old woman with dyspnea and cTn-elevation within the first days following acute ischemic stroke and discuss potential differential diagnoses and diagnostic dilemmas.

Keywords

Acute ischemic stroke, neurocardiogenic interactions, stroke-heart syndrome, cardiac troponin

Date received: 24 March 2023; accepted: 6 June 2023

Introduction

It was more than 80 years ago when it was recognized that heart damage and dysfunction, electrocardiographic abnormalities, and arrhythmias could be caused by cerebrovascular disease.[1] Moreover, within the last decade, experimental and clinical studies have convincingly highlighted a cross-talk between the heart and the brain in patients with acute ischemic stroke (AIS).[2] As such, although a cardiac disease may not be preexisting before the onset of AIS, severe cardiac complications can commonly occur in the acute phase of AIS, worsening outcomes, and prognosis.[2] Indeed, accumulating evidence suggests that the main causes of mortality after AIS include neurological damage and cardiovascular complications, such as heart failure, hemodynamic disturbances, and instability, left ventricular systolic dysfunction, diastolic dysfunction, electrocardiographic anomalies, arrhythmias, and cardiac arrest.[3,4] In recent years, various pathophysiological mechanisms explaining the stroke-heart interactions have been suggested, including autonomic dysfunction and sympathetic overdrive, inflammatory responses and thromboinflammation, destruction of the blood-brain-barrier, vascular endothelial dysfunction, and oxidative stress, which could potentially serve as therapeutic targets.[5,6] Furthermore, the pathophysiological processes and clinical manifestations—cTn elevation included—as a consequence of neurocardiogenic interactions in patients with AIS have been recently summarized under the concept of "stroke-heart syndrome."[6,7] Although cTn-elevation can be commonly found in patients with AIS, its differential diagnosis frequently remains complex.[7] Here, we report a case of a dynamic cTn-elevation within the first days after the onset of AIS, and we discuss the potential aspects of the underlying causes.

Case presentation

An 86-year-old woman was admitted to our department after hospitalization in the allocated stroke center due to acute right carotid artery occlusion and ischemic stroke in the middle cerebral artery (MCA) territory treated with intravenous thrombolysis and stenting of the right carotid artery. Brain magnetic resonance imaging after bridging therapy with successful revascularization showed ischemic lesions in the precentral and postcentral gyrus but also in the posterior border zone, in the amygdala and hippocampus, as well as multiterritorial, multiterritorial bihemispheric and bicerebellar small volume ischemic lesions of presumed periinterventional embolic origin were additionally observed (Figure 1).

[1]Department of Internal Medicine, Thun Hospital, Thun, Switzerland
[2]Department of Neurology, Thun Hospital, Thun, Switzerland
[3]Department of Cardiology, Thun Hospital, Thun, Switzerland

Corresponding Author:
Mairi Ziaka, Department of Internal Medicine, Thun Hospital, Krankenhausstrasse 12, Thun 3600, Switzerland.
Email: mairi.ziaka@gmail.com

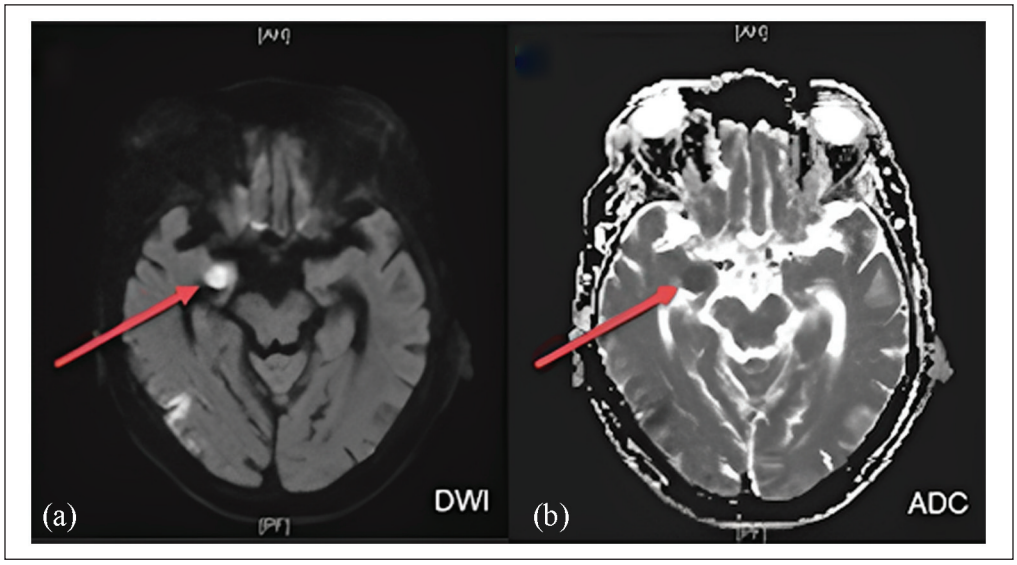

Figure 1. (a) Brain MRI diffusion weighted imaging (DWI). (b) Corresponding low apparent diffusion coefficient (ADC) values. Both panels refer to Day 2 after stroke and show exemplary ischaemic lesions in right amygdala (red arrows).
MRI: Magnetic Resonance Imaging.

Table 1. Laboratory data on admission and hospital day 3.

Variable	Reference range *(Adults)*	On admission	Hospital day 3
Haematocrit (%)	36–44	32	27.1
Hemoglobin (g/dL)	12.1–15.4	10.2	8.2
White-cell count (per uL)	3000–10,500	22,800	8950
Platelet count (per uL)	150,000–450,000	483,000	339,000
C-reactive protein (mg/L)	<5	7	100
Cardiac troponin (ng/L)	<14	28	120
NT-pro-BNP (pg/mL)	<738	470	5279

The data presented for the two measurement points were performed by different laboratories.
BNP, brain natriuretic peptide; NT-pro-BNP, N-terminal proBNP.

Documented National Institutes of Health Stroke Scale (NIHSS)[8] did not change remarkably after reperfusion treatment (i.e. pre-treatment NIHSS = 5; post-treatment NIHSS on Day 2 = 6). At hospital admission to our hospital and 2 days after the stroke, the current medical therapy included acetylsalicylic acid, clopidogrel, and lisinopril. The patient was found to be in poor general condition with marked hypertension, tachycardia, respiratory distress, and desaturation down to 93%—despite receiving 2 L/min oxygen via nasal cannula. Neurologic examination demonstrated left hemineglect, dysarthria, and slight left-sided sensorimotor dysfunction on the left. Laboratory parameters showed anemia, normal leucocyte count, elevated C-reactive protein and blood sedimentation rate, marked proteinuria (protein to creatinine ratio 512.12 mg/mmol), and significant albuminuria (albumin-to-creatinine ratio 377.27 mg/mmol) (Table 1). Chest X-ray showed a small opacity in the left hilus and signs of hypervolemia.

After considering aspiration pneumonia, antibiotic treatment with amoxicillin/clavulanic acid was initiated. On Day 2, after admission, a chest computer tomography was performed to exclude pulmonary embolism due to aggravation of dyspnea and persistent oxygen desaturations. The results revealed no pulmonary embolism but small bilateral pleural effusions, atelectasis, and bilateral opacities. At this point (i.e. Day 3 after stroke), the laboratory tests showed an elevated cTn of 120 ng/L (cTn at Day 0 was 28 ng/L) with further dynamic change after 3 hours (149 ng/L) and an elevated pro-brain natriuretic peptide (NT-pro-BNP, 5279 pg/mL; Table 1- The *measurement performed with a sandwich fluorescent immuno-reaction assay.*).

A 12-lead electrocardiogram (ECG) revealed a sinus rhythm at 110 bpm, normal atrioventricular and intraventricular conduction, and the absence of ST-T segment abnormalities. Echocardiography demonstrated a hypertrophic left ventricle

with preserved ejection fraction (EF) without evidence of intracardiac thrombi or wall motion abnormalities.

Based on the diagnosis of neurocardiogenic non-ischemic myocardial injury with concomitant pulmonary edema, furosemide, and metoprolol were added to the pre-existing medication. Respecting the wish of the patient and her family, we decided against coronary angiography. The patient survived the acute stage and was discharged to a nursing home in improved—although still reduced—general condition. Regarding severe proteinuria and albuminuria, protein electrophoresis raised the suspicion of an immunoglobulin A (IgA)-type multiple myeloma; the patient, however, refused further investigation and therapy.

Discussion

Although the described case report represents an everyday medical condition, the presence of elevated cTn in patients with AIS is often a challenge for clinicians and may influence the development of hypotheses related to the underlying causes of the concomitance of acute cardiac damage in AIS patients.

Indeed, it is convincingly recognized that AIS may cause severe cardiac dysfunction, which refers to neurocardiogenic interactions in this population[2] and represents more complex pathophysiological mechanisms than traditional vascular risk factors.[6] Cardiac injury is a common medical problem during the acute phase of AIS[9] and includes a variety of clinical manifestations, that is, post-stroke acute coronary syndromes (ACS; type 1 and 2 myocardial infarction, MI), acute myocardial injury—ischemic and non-ischemic—as presented by cTn-elevation, left ventricular dysfunction of varying severity up to heart failure, and stroke-associated Takotsubo Syndrome,[2] ECG-alterations such as QT-interval prolongation, T-wave inversion, and ST-depression, tachyarrhythmias including atrial fibrillation,[2] and sudden cardiac death.[6]

In order to early detect the cardioembolic origin of stroke and to identify patients at high risk of cardiac complications and poor outcomes, quantitative cTn-determination in all patients with suspected stroke is strongly recommended.[4] However, MI-type 1 and 2 is only one of the possible etiologies of elevated cTn in the acute phase of ischemic stroke.[7] As a consequence, it can result in differential diagnosis dilemmas and influence the appropriate management.[6]

Indeed, the elevation of cTn in the first hours to days after the onset of AIS may be part of the recently described "stroke-heart syndrome," which subsumes the entire spectrum of stroke-induced cardiac disturbances within the first 30 days after AIS and includes acute cardiac injury and dysfunction as well as arrhythmias.[7] In this case, correct clinical diagnosis is of critical importance given the fact that the treatment of ACS can lead to bleeding complications[7] with potentially devastating consequences in this particular patient population. Moreover, cTn elevation may reflect left ventricular dysfunction.[10] Indeed, moderate impaired left ventricular fraction, that is, EF $< 55\%$, is observed in 8%–12% of the patients with mild-to-moderate ischemic events, whereas severe left ventricular dysfunction with EF less than 40% occurs in 3%–8% of the patients.[9] Serial cTn measurements estimating dynamic changes are suggested[6,7] to differentiate between chronic and acute cardiac injury.

The related pathophysiological mechanisms of the "stroke-heart syndrome" are complex and include autonomic dysregulation, catecholamine release, stroke-induced dysfunction of the hypothalamic-pituitary-adrenal axis, local and systemic inflammatory reactions, myocyte damage, and others (Figure 2).[2] Ischemic events involving the right insular cortex—regulating autonomic connection to the heart—are part of stroke characteristics that have attracted much attention as a potential strong trigger of neurocardiogenic dysfunction.[2] Further related regions include the hippocampus, amygdala, hypothalamus, and brainstem.[6] Despite that data regarding key mediators involved in the pathophysiology of stroke-heart syndrome are scarce, accumulating evidence stemming mostly from experimental studies supports the hypothesis that autonomic dysregulation and inflammation represent pathogenetic pillars for the development of cardiac complications in patients with AIS.[9,11,12] Indeed, experimental data of cardiac dysfunction in models of acute brain injury indicate peripheral sympathetic hyperactivity, as suggested by the elevated levels of catecholamines in serum and heart in animals,[13,14] which could potentially lead to myocardial toxicity and coronary microvascular spasm.[15] This hypothesis is further supported by clinical studies in patients with Takotsubo cardiomyopathy showing a two- to threefold increase in the levels of catecholamines compared to patients with acute myocardial infarction and a 20-fold increase compared to healthy individuals.[16] Interestingly, catecholamine release occurs within minutes after stroke.[17,18] Stroke-induced catecholamine elevation is related to a variety of pathophysiological mechanisms, for example, direct release from the sympathetic nerve and myocardial nerve endings[19–21] enhanced release from the adrenal glands due to the autonomic dysregulation,[19] elevated delivery of adrenocorticotropic hormone,[22] and cytokine-mediated increases by the production of inflammatory mediators impairing the hypothalamic-pituitary-adrenal (HPA) axis.[23] Catecholamines bind to β1 adrenoreceptors, alter intracellular calcium levels, influence the synthesis of adenosine triphosphate synthesis, and mediate oxidative stress and osmotic swelling, leading to myocardial cell death.[24] Moreover, they induce endothelial dysfunction, enhance oxygen demand, contribute to coronary atherogenesis, and make plaques more vulnerable to rupture.[11] Furthermore, the proximity of cardiomyocytes and nerve endings facilitates the enhanced local activity of catecholamines disturbing calcium homeostasis and leading to impaired β-adrenergic signal transduction, which results in myocardial contraction band necrosis and altered coronary microcirculation.[15,25,26] In addition, an excess of catecholamines, particularly epinephrine, may be characterized

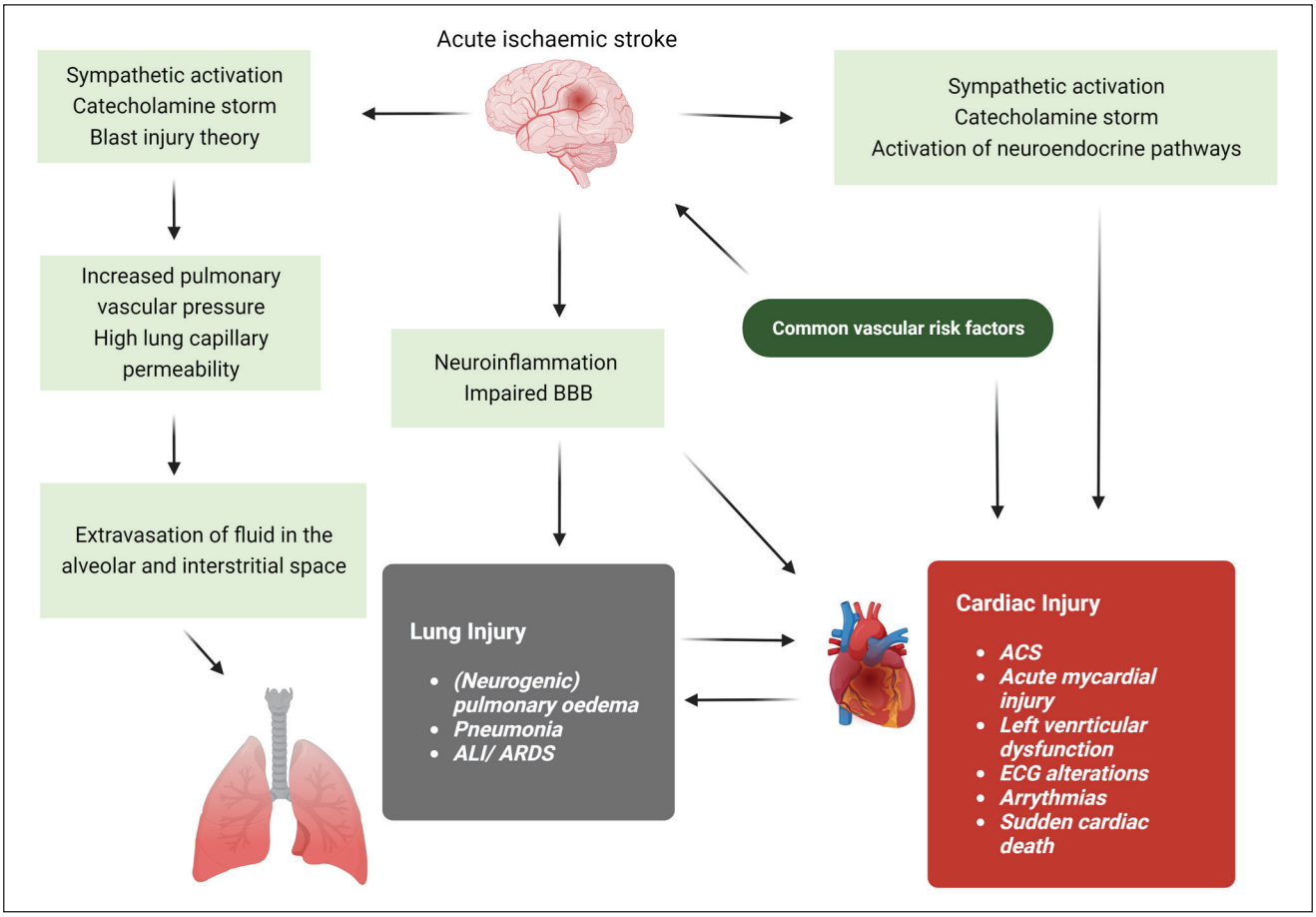

Figure 2. Simplified schematic representation of the pathophysiology of pulmonary and cardiac complications in patients with acute ischaemic stroke.
ACS: Acute Coronary Syndrome; ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; BBB: Blood Brain Barrier.

by a negative inotropic effect as they mediate the switching of β-2 adrenergic receptors from the physiological G-protein-activated cardiostimulant to inhibitory G-protein-activated cardiodepressant pathways.[2,27] Therefore, targeting local cardiac catecholamine using β-blockers during an ischemic event's acute phase seems conclusive and should be further examined in well-designed randomized and blinded therapy studies.[6]

Besides sympathetic overdrive, pro-inflammatory cascades are well-recognized contributors to the stroke-heart syndrome.[2] The inflammatory response occurs immediately after the onset of stroke and represents a pathophysiological cornerstone of stroke progression.[28] Even though pro-inflammatory and pro-coagulative mediators are released within minutes after the ischemic event, their plasma elevation is only temporary.[29,30] Interestingly, myocardial damage continues over time despite the decrease in their plasmatic concentration.[30] Moreover, it has been convincingly demonstrated that acute ischemic cerebral events are associated with BBB disruption allowing the recruitment of peripheral cells, thus, resulting in neuroinflammation. The local inflammatory cascade is characterized by the release of cytokines and chemokines, astrogliosis, microgliosis, and activation of endothelial cells.[29,31] Furthermore, there is mounting evidence indicating that pro-inflammatory mediators, for example, interleukin (IL)-1β, IL-6, and tumor necrosis factor α, adhesion molecules, integrins, and chemokines can further disrupt BBB and lead to systemic inflammation[32,33] affecting several organs and symptoms including the heart.[2,34] In addition, excessive catecholamine levels stimulate the release of IL-1β by macrophages which in turn worsens local inflammation due to the recruitment of pro-inflammatory leukocytes.[23] Finally, the overexpression of pro-inflammatory mediators from the disrupted neuronal cells may cause further sympathetic alterations, which influence the HPA axis leading to further catecholamine elevation.[9]

Our patient had a right-sided MCA territory infarction involving the amygdala and the hippocampus. Both regions regulate the central autonomic function and play an integral role in the pathophysiology of the "stroke-heart syndrome."[2,6] In the case of our patient and based on the absence of clinical symptoms, ECG-changes, and wall motion abnormalities, we estimate that cTn-elevation was due to a stroke-induced neurocardiogenic non-ischemic myocardial injury caused either by microcirculatory dysfunction (i.e. endothelial or oxidative

stress) or by myocardial demand ischemia precipitated by hypertensive crisis, tachycardia, and respiratory distress.[2,34] However, given that coronary angiography or CT-coronary angiography were not performed in our patient, other causes of dynamic troponin elevation, such as non-STE-myocardial infarction with non-obstructive coronary arteries (MINOCA), could not be definitively excluded. Indeed, the need for specific algorithms—if possible without invasive procedures—represents a scientific challenge to differentiate etiological causes and pathophysiological mechanisms of cardiac troponin elevation in patients with acute ischemic stroke. The PRAISE study (Prediction of Acute Coronary Syndrome in Acute Ischemic Stroke) aims to clear up this question by studying patients with acute ischemic stroke with significant cTn elevation by preparing coronary angiography complementary to the implementation of electrocardiography and echocardiography.[35]

Conclusion

If not properly assessed, cTn elevation in the acute phase of AIS is challenging and can delay the right diagnosis and management. Enhanced cTn levels with dynamic changes in the first 30 days and especially in the first 72 h following stroke may occur due to ACS co-existence. Importantly, the same clinical manifestation may additionally represent the expression of the "stroke-heart syndrome." Careful differential diagnosis based on clinical, laboratory, ECG, and echocardiographic criteria and interdisciplinary collaboration between healthcare practitioners is highly encouraged to ensure quality and safety in the management of this complex patient population.

Acknowledgements

We thank the Department of Neurology of the University Hospital of Bern for providing the imaging and initial laboratory findings. Figure 2 created with BioRender.com

Author contributions

The study was designed by M.Z., K.H., A.G., I.B., and M.Z. were involved in the diagnosis and management. K.H., A.G., and M.Z. searched the articles and drafted the manuscript. All authors read and approved the final manuscript.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Publication costs for this article were funded by the authors' institutions.

Ethical approval

The project did not meet the definition of human subject research. Ethical approval was not required for this case report in accordance with local or national guidelines.

Informed consent

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

ORCID iD

Mairi Ziaka https://orcid.org/0000-0001-5298-7925

References

1. Byer ER, Ashman R and Toth LA. Electrocardiograms with large, upright T waves and long Q-T intervals. *Am Heart J* 1947; 33(6): 796–806.
2. Ziaka M and Exadaktylos A. The heart is at risk: understanding stroke-heart-brain interactions with focus on neurogenic stress cardiomyopathy-a review. *J Stroke* 2023; 25(1): 39–54.
3. Chen Z, Venkat P, Seyfried D, et al. Brain-heart interaction: cardiac complications after stroke. *Circ Res* 2017; 121(4): 451–468.
4. Battaglini D, Robba C, Silva ALD, et al. Brain-heart interaction after acute ischemic stroke. *Crit Care* 2020; 24(1): 163.
5. Wang M and Peng Y. Advances in brain-heart syndrome: attention to cardiac complications after ischemic stroke. *Front Mol Neurosci* 2022; 15: 1053478.
6. Scheitz JF, Sposato LA, Menger JS, et al. Stroke-heart syndrome: recent advances and challenges. *J Am Heart Assoc* 2022; 11(17): e026528.
7. Scheitz JF, Stengl H, Nolte CH, et al. Neurological update: use of cardiac troponin in patients with stroke. *J Neurol* 2021; 268(6): 2284–2292.
8. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; 20(7): 864–870.
9. Scheitz JF, Nolte CH, Doehner W, et al. Stroke-heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol* 2018; 17(12): 1109–1120.
10. Weil BR, Suzuki G, Young RF, et al. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *J Am Coll Cardiol* 2018; 71(25): 2906–2916.
11. Sposato LA, Hilz MJ, Aspberg S, et al. Post-stroke cardiovascular complications and neurogenic cardiac injury: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; 76(23): 2768–2785.
12. Dorrance AM and Fink G. Effects of stroke on the autonomic nervous system. *Compr Physiol* 2015; 5(3): 1241–1263.
13. Bieber M, Werner RA, Tanai E, et al. Stroke-induced chronic systolic dysfunction driven by sympathetic overactivity. *Ann Neurol* 2017; 82(5): 729–743.
14. Min J, Farooq MU, Greenberg E, et al. Cardiac dysfunction after left permanent cerebral focal ischemia: the brain and heart connection. *Stroke* 2009; 40(7): 2560–2563.
15. Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of takotsubo syndrome. *Circulation* 2017; 135(24): 2426–2441.

16. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; 352(6): 539–548.
17. Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. *Stroke* 2002; 33(6): 1671–1676.
18. Meloux A, Rigal E, Rochette L, et al. Ischemic stroke increases heart vulnerability to ischemia-reperfusion and alters myocardial cardioprotective pathways. *Stroke* 2018; 49(11): 2752–2760.
19. Mertes PM, Carteaux JP, Jaboin Y, et al. Estimation of myocardial interstitial norepinephrine release after brain death using cardiac microdialysis. *Transplantation* 1994; 57(3): 371–377.
20. Eitel I, Brenkenhoff FVK, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011; 306(3): 277–286.
21. Nef HM, Möllmann H, Hilpert P, et al. Activated cell survival cascade protects cardiomyocytes from cell death in Tako-Tsubo cardiomyopathy. *Eur J Heart Fail* 2009; 11(8): 758–764.
22. Fassbender K, Schmidt R, Mössner R, et al. Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. relation to acute confusional state, extent of brain damage, and clinical outcome. *Stroke* 1994; 25(6): 1105–1108.
23. Sobowale OA, Parry-Jones AR, Smith CJ, et al. Interleukin-1 in stroke: from bench to bedside. *Stroke* 2016; 47(8): 2160–2167.
24. Gopinath R and Ayya SS. Neurogenic stress cardiomyopathy: what do we need to know. *Ann Card Anaesth* 2018; 21(3): 228–234.
25. Ghadri JR, Wittstein IR, Prasad A, et al. International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018; 39(22): 2032–2046.
26. White M, Wiechmann RJ, Roden RL, et al. Cardiac beta-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury. Evidence for catecholamine-mediated myocardial damage. *Circulation* 1995; 92(8): 2183–2189.
27. Paur H, Wright PT, Sikkel MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. *Circulation* 2012; 126(6): 697–706.
28. Fu Y, Liu Q, Anrather J, et al. Immune interventions in stroke. *Nat Rev Neurol* 2015; 11(9): 524–535.
29. Santos Samary C, Pelosi P, Silva PL, et al. Immunomodulation after ischemic stroke: potential mechanisms and implications for therapy. *Crit Care* 2016; 20(1): 391.
30. Balint B, Jaremak V, Thorburn V, et al. Left atrial microvascular endothelial dysfunction, myocardial inflammation and fibrosis after selective insular cortex ischemic stroke. *Int J Cardiol* 2019; 292: 148–155.
31. Turner RJ and Sharp FR. Implications of MMP9 for blood brain barrier disruption and hemorrhagic transformation following ischemic stroke. *Front Cell Neurosci* 2016; 10: 56.
32. Yilmaz G and Granger DN. Leukocyte recruitment and ischemic brain injury. *Neuromolecular Med* 2010; 12(2): 193–204.
33. Liesz A, Zhou W, Mracskó É, et al. Inhibition of lymphocyte trafficking shields the brain against deleterious neuroinflammation after stroke. *Brain* 2011; 134(pt 3): 704–720.
34. Ziaka M and Exadaktylos A. Brain-lung interactions and mechanical ventilation in patients with isolated brain injury. *Crit Care* 2021; 25(1): 358.
35. Nolte CH, Rennenberg RV, Litmeier S, et al. PRediction of acute coronary syndrome in acute ischemic StrokE (PRAISE)—protocol of a prospective, multicenter trial with central reading and predefined endpoints. *BMC Neurol* 2020; 20(1): 318.