British Journal of Anaesthesia **112** (5): 803–15 (2014)
Advance Access publication 17 March 2014 · doi:10.1093/bja/aeu046

BJA

Brain–heart crosstalk: the many faces of stress-related cardiomyopathy syndromes in anaesthesia and intensive care

A. T. Mazzeo[1]*, A. Micalizzi[2], L. Mascia[1], A. Scicolone[3] and L. Siracusano[2]

[1] Department of Anaesthesia and Intensive Care, University of Torino, Azienda Ospedaliera Citta' della Salute e della Scienza di Torino, Presidio Molinette, Corso Dogliotti 14, 10126 Torino, Italy
[2] Department of Neuroscience, Psychiatric and Anaesthesiological Sciences, University of Messina, Via Consolare Valeria, Messina, Italy
[3] Department of Anaesthesia and Intensive Care, University of Piemonte Orientale 'Amedeo Avogadro', Ospedale Maggiore della Carita', Corso Giuseppe Mazzini 18, 28100 Novara, Italy

* Corresponding author. E-mail: anna.mazzeo@unito.it

Editor's key points

- Neurogenic stress can lead to a number of cardiac problems.
- The authors have reviewed the pathophysiology and clinical management of these problems.
- Prevention and prompt management of cardiac problems during neurogenic stress are crucial in improving outcomes.

Neurogenic stress cardiomyopathy (NSC) is a well-known syndrome complicating the early phase after an acute brain injury, potentially affecting outcomes. This article is a review of recent data on the putative role of localization and lateralization of brain lesions in NSC, cardiac innervation abnormalities, and new polymorphisms and other genetic causes of the sympathetic nervous system over-activity. Concerns regarding the management of stress-related cardiomyopathy syndromes during the perioperative period are also discussed. Future clinical research should explore whether specific factors explain different patient susceptibilities to the disease and should be directed towards early identification and stratification of patients at risk, so that such patients can be more carefully monitored and appropriately managed in critical care and during the perioperative period.

Keywords: brain injuries; receptor cross-talk; stress cardiomyopathy; subarachnoid haemorrhage; sympathetic nervous system

In the emerging field of organ crosstalk,[1] brain–heart interconnections[2] in the critically ill neurological patient hold a preeminent position, with clinically relevant implications in the intensive care unit (ICU) and during the perioperative period.

'Neurogenic stunned myocardium', also called 'neurogenic stress cardiomyopathy' (NSC),[3] is a syndrome that can occur after severe acute neurologic injury, such as subarachnoid haemorrhage (SAH),[4 5] traumatic brain injury,[6] ischaemic or haemorrhagic stroke,[7] central nervous system infections,[8] epileptic seizures,[9] or any sudden stressful event.[3 10 11] The cardiac involvement is expressed either in terms of electrocardiographic (ECG) signs with Q-T interval prolongation, long Q-T syndrome and torsade de points, S-T-segment depression, T-wave inversion, and ventricular and supraventricular arrhythmias, or in the form of left ventricular (LV) wall motion abnormalities, myocardial necrosis enzyme release, and increased B-type natriuretic peptide (BNP).[3 11 12]

ECG abnormalities occur in 25–75% of SAH patients and arrhythmias are present in ~100% of patients.[12] Serum markers of cardiac injury are increased in 20–30% of patients with the most severe grades of SAH and wall motion abnormalities occur in 8–13% of patients with regional or global kinetic patterns.[3 13–16] Wall motion abnormalities generally occur early in the course of SAH, within the first 2 days, their prevalence declining 3–8 days after the SAH.[5] After acute ischaemic stroke, 1.2% incidence of NSC is described.[7] Neurocardiogenic injury is less common in other forms of acute brain injury, but a high index of suspicion is still required in patients with acute cardiac abnormalities occurring in the acute phase after admission. Neurocardiogenic injury is in fact associated with an increased risk of all-cause mortality [hazard ratio (HR): 5.3; confidence interval (CI): 3.0–9.3], cardiac mortality (HR: 7.3; CI: 1.7–31.6), and heart failure (HR: 4.3; CI: 1.53–11.88).[17]

Despite high morbidity and mortality,[18 17] NSC management is mainly supportive and symptomatic, based on the treatment of life-threatening events (such as malignant arrhythmias or cardiogenic shock). The ability to identify early patients at risk of cardiac complications after acute brain injury by better elucidating the inherent pathological mechanisms could help to improve outcomes, especially if associated with close monitoring and aggressive treatment, although no data are currently available to indicate that a proactive rather than simple support strategy is better in the care of patients with NSC.

The growing interest of anaesthesiologists in stress-related cardiomyopathy syndromes is the result of an increasing number of cases of this syndrome, traditionally 'confined' to the critical care and cardiology literature, being reported in the anaesthesiology literature and the real need to address several unanswered questions, such as the true incidence of the syndrome, the multifactorial pathogenesis, individual

susceptibility, the role of perioperative medications, and optimal anaesthetic management.[19]

Pathophysiology

NSC is part of the stress-related cardiomyopathy syndrome spectrum,[20–23] which also includes the Takotsubo syndrome[24] with its typical apical and mid-ventricular dysfunction and significant overlap with NSC in clinical appearance, underlying pathophysiology and reversibility.

NSC is a cardiomyopathy syndrome secondary to structural or functional brain damage. The term NSC reflects the underlying pathophysiology of myocardial dysfunction related to the stress of catecholamine excess, triggered by an acute neurological injury. Takotsubo cardiomyopathy, in contrast, relates to the primary form of stress-related cardiomyopathy syndrome specifically related to emotional or physical stress situations and is the syndrome more frequently observed during anaesthesia.

Many theories for stress-related cardiomyopathy syndrome have been described: (i) transient multi-vessel coronary artery spasm; (ii) microvascular dysfunction; (iii) aborted myocardial infarction with spontaneous coronary thrombus lysis;[25] and (iv) the 'catecholamine hypothesis'.[3] Observational studies and experimental models have failed to demonstrate strong validity of the first three theories, with only a few reports in recent literature,[25 26] whereas the 'catecholamine hypothesis', consistent with catecholamine-mediated direct myocardial injury, is widely accepted.[24 27] Indeed, the increased sympathetic activity could also explain the diffuse coronary microvascular dysfunction, the multi-vessel epicardial spasm, the transient dynamic LV outflow tract obstruction and, perhaps, the presence of coronary clots undergoing spontaneous recanalization.[28] It is also possible that a spectrum of various pathogenetic factors, not mutually exclusive, ranging from overt or subtle neurogenic injury, acute coronary dysfunction, excess exogenous or endogenous catecholamines and a particular genetic basis with polymorphisms of $\beta1$, $\beta2$, $\alpha2$ receptors, G_s or G_i proteins,[29] adenyl-cyclase or other downstream components of the biochemical adrenergic pathways, may play a role in stress-related cardiomyopathy syndrome.

However, the 'catecholamine hypothesis' (illustrated in Fig. 1) seems the most likely candidate. Structural brain damage and a sudden increase in intracranial pressure induce an autonomic storm with elevation in tissue and plasma catecholamine levels. Indeed, a three-fold increase in total body norepinephrine spill into the plasma is described within the first 48 h of SAH, and these levels can still be elevated after 1 week.[30] In particular, high myocardial interstitial concentrations of norepinephrine result in myocyte calcium overload and cell death causing cardiac dysfunction.[24 31] Experimental studies show not only an immediate enhancement of activity in sympathetic nerve terminals with massive release of catecholamines into the cardiac tissue,[27 31 32] and a small leak into the systemic circulation, but also increased sensitivity to norepinephrine infusion.[33] In experimental models of brain death induced by intracranial hypertension in baboons, cardiac abnormalities were blocked by cardiac sympathectomy or denervation, but still occurred after bilateral adrenalectomy, thus supporting the endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than circulating catecholamines as the mediator of neurocardiogenic injury.[32] In an experimental model of SAH in dogs, plasma concentrations of norepinephrine and epinephrine increased significantly from 120 and 130 pg ml^{-1} before SAH to 1700 and 5600 pg ml^{-1} at 5 min after SAH.[27] In the case of myocardial stunning due to sudden emotional stress, plasma catecholamine levels at presentation were 2–3 times higher than the values measured in patients with Killip class III myocardial infarction and 7–34 times normal values: median epinephrine levels were 1264, 376, and 37 pg ml^{-1}, respectively; median norepinephrine levels were 2284,1100, and 169 pg ml^{-1}, respectively.[22] These high concentrations of catecholamines lead to calcium overload into myocardial cells, free

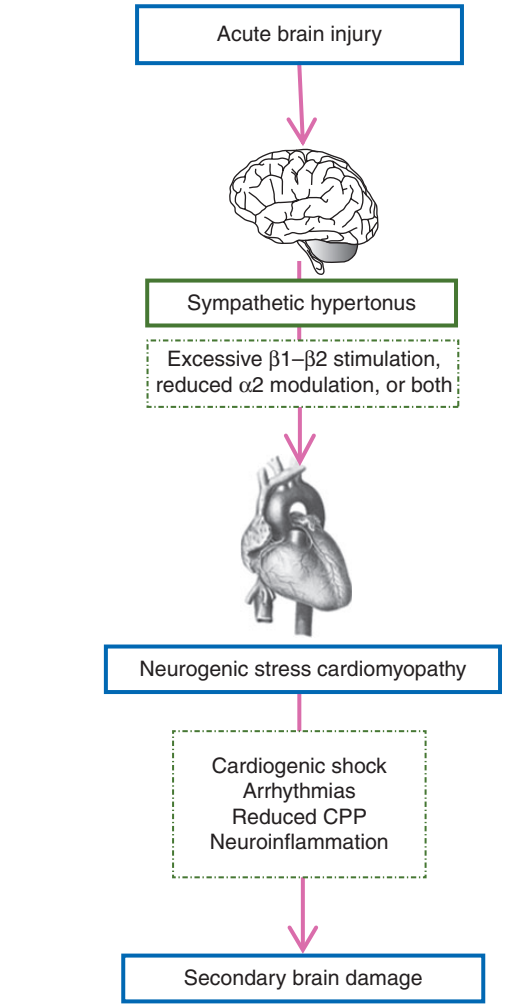

Fig 1 A schematic illustration of the 'catecholamine hypothesis mechanism' responsible for neurogenic stress cardiomyopathy after acute brain injury. Neurocardiogenic injury can induce secondary brain damage by impaired systemic and brain homeostasis. CPP, cerebral perfusion pressure.