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

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In the emerging field of organ crosstalk,1 brain–heart interconnections2 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.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 syndrome24 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 sympathetetic 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 reca-nalization.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 β1, β2, α2 receptors, Gα or Gi 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.31–33 Experimental studies show not only an immediate enhancement of activity in sympathetic nerve terminals with massive release of catecholamines into the cardiac tissue,29 30 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 228, 1100, and 169 pg ml⁻¹, respectively.32 These high concentrations of catecholamines lead to calcium overload into myocardial cells, free

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**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.
radical production, and adenosine triphosphate depletion, with resulting ECG changes, failure of myocardial contraction, and possible cell death.20 31 34 35

In patients with extreme sympathetic discharge, a specific tissue lesion called ‘myocardial contraction band necrosis’ has been described, characterized by hypercontraction of sarcomeric myofibrils, eosinophilic transverse bands, and interstitial mononuclear infiltration.2 Histological changes in NSC are characterized by myocardial disarray secondary to catecholamine overload with a significant increase in extracellular matrix protein, contraction band necrosis, mild inflammatory cell infiltration, fibrotic changes, and increase in the collagen I/III ratio due to high levels of the pro-fibrotic mediators, angiotensin II, and free radicals.21

The differences between the myocardial damage of ischaemic disease and that of NSC are significant: with ischaemic disease, cells die in a relaxed state with a polymorphonuclear cell response and necrosis in the compromised vascular territory; in NSC, cells die in a hyper-contracted state with contraction bands and early calcification and myofibrillar lesions, which are visible within minutes of onset, appearing close to cardiac nerves. Furthermore, in NSC, the regional wall motion abnormalities extend beyond a single epicardial vascular distribution and are reversible.36

A role for inflammation among the mechanisms contributing to the myocardial injury of NSC has also been proposed.37 38 While acetylcholine inhibits the release of pro-inflammatory cytokines, parasympathetic dysfunction may facilitate uncontrolled inflammation, causing myocardial damage.37 Furthermore, elevated levels of cytokines have been described in the cerebrospinal fluid and serum of SAH patients, contributing to neurocardiogenic damage.39

Although the occurrence of NSC after acute brain injury is well recognized, research still needs to address several unanswered questions, such as why only certain subgroups of patients with acute brain injury develop NSC, whether or not we can identify patients at risk early in the process, and whether localization and lateralization of brain lesions may affect the occurrence and the severity of cardiac dysfunction.

Furthermore, the anaesthetic challenges of the neurologically critically ill patient presenting with NSC, the possible occurrence of myocardial stunning during anaesthesia, and the impact of anaesthesia on the autonomic nervous system (ANS) during the perioperative period have not been fully explored.

The ‘head’ of the problem

Neurocardiogenic injury and the insula

The cardiovascular system responds to challenging clinical conditions through a series of well-regulated neural mechanisms involving several cardio-regulatory sympathetic pathways (Fig. 2) that enable the cardiovascular function to adapt to different challenges. The hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullary axes are the main biological systems activated during the stress response23 that result in neuroendocrine changes, including an increase in epinephrine and norepinephrine levels. In the last decade a network within the insular cortex, the anterior cingulate gyrus and the amygdala, has been found to play a pivotal role in the brain–heart axis.50 The insular cortex has a deep anatomical location (Fig. 3), lying at the base of the Sylvian fissure, and in primates it has numerous connections with the cerebral cortex, the basal ganglia, and the limbic structure.61 62 Experimental and clinical studies have shown that the insular cortex plays a crucial role in the integration of autonomic function. The existence of lateralization for cardiovascular function, with sympathetic tone predominantly regulated in the right insular region and parasympathetic effects situated in the left insula, is supported by several studies.18 40 42 44–47 Electrical stimulation of the insula produces cardiovascular changes in rats, monkeys,18 and humans, depending on the side of stimulation.44 45 Bradycardia or a depressant effect (on diastolic arterial pressure) was more frequent with stimulation of the left insular cortex, whereas tachycardia or a pressor effect was elicited if the right insula was stimulated.44 Furthermore, the anterior part of the insular cortex subserves emotional functions, whereas the posterior part subserves ascending visceral symptoms.42

In clinical studies, insular cortex damage has been associated with ECG changes, arrhythmias, impaired cardiac wall motion, and with a poor outcome.50 63 In patients with acute ischaemic stroke, ischaemia of the right insular cortex was associated with higher arterial pressure and norepinephrine levels47 and there was a relationship between right insular cortex lesions, ECG abnormalities, and increased risk of mortality at 3 months.49 Other studies also showed that left insular cortex injury can be associated with cardiac dysfunction and myocardial wall motion impairment.45

The mechanism of NSC after acute brain injury may be related to disinhibition of the right insular cortex and a resulting augmentation of sympathetic tone.50 A shift in cardiac autonomic balance towards sympathetic predominance, and subsequent decreased cardiac wall motion and alterations in cardiac rhythm may be the cause of increased cardiac morbidity in patients with left insular stroke, compared with other sites of injury.40 45 However, others reported a major role of the right insula in the pathogenesis of NSC, and an association with more complex arrhythmias than found in any other localization.69 51 The fact that the insular cortex is located in the region of the middle cerebral arteries may explain its frequent involvement in cerebrovascular accidents.40 50

Thus, evaluation of insular involvement with focused neuroimaging techniques could help stratify the relative risk of adverse outcomes when assessing a patient with acute brain injury, suggesting close cardiac monitoring.53

The ‘heart’ of the problem

Cardiac innervation

Cardiac innervation abnormalities are described in several pathologies, including cardiac amyloidosis,54 dilated cardiomyopathy,55 Parkinson’s disease,56 and Lewy body dementia.57 In patients with acute brain injury, different patterns of global or regional LV wall motion abnormalities have been
described, which do not match typical coronary artery distribution.58 In some patients, LV kinetic abnormalities involve the apical region,59 as in Takotsubo syndrome.34 A possible explanation for this is related to the fact that the apex is structurally more vulnerable to catecholamine-mediated toxicity than the basal regions, because of a larger proportion of \( \beta_2 \)- than \( \beta_1 \)-adrenergic receptors and greater \( \beta_2 \)-adrenergic receptor-induced sensitivity in the apex than in basal cardiomyocytes.60 29 Other authors have described a pattern of ‘apex sparing’ in > 50% of cases of NSC after SAH: this pattern is characterized by contraction abnormalities in the basal and mid-ventricular portions of the LV wall, with no involvement of the apex,61 62
probably because of the paucity of sympathetic nerve terminals in the apex.\textsuperscript{53, 64}

A combined evaluation of myocardial sympathetic innervation, myocardial perfusion, and LV systolic function in patients with SAH can provide a more comprehensive assessment of LV dysfunction.\textsuperscript{6} Cardiac innervation can be studied \textit{in vivo} with metaiodobenzylguanidine (MIBG), a scintigraphic marker of norepinephrine, and denervation is seen as a reduction in MIBG uptake.\textsuperscript{65}

Echocardiography and myocardial scintigraphy with technetium sestamibi and MIBG performed in SAH patients to simultaneously evaluate LV systolic function, myocardial perfusion, and sympathetic innervation demonstrated in 29\% of the patients evidence of sympathetic functional denervation, whereas none had perfusion deficits.\textsuperscript{4} A correlation between regional wall motion abnormalities and altered MIBG uptake was also demonstrated.\textsuperscript{4} Increased catecholamine concentrations in the cardiac tissue may lead to myocyte necrosis with related cardiac contractile dysfunction and damage to the same sympathetic nerve terminals.\textsuperscript{4} However, it is possible that the cardiac damage is secondary to neuronal degeneration caused by the effects of the SAH on the origin of the sympathetic path to the heart, such as in the insula or the hypothalamus, as supported by the related clinical model of myocardial dysfunction in brain-dead donor organs.\textsuperscript{66}

The study of cardiac innervation early after neurogenic injury could help to clarify its role in NSC genesis and to investigate the relationships between cardiac innervation and the corresponding patterns of LV dysfunction, thus representing an intriguing area for future research.

**Polymorphisms of adrenergic receptors**

Cardiac responsiveness to catecholamines is affected by genetic polymorphisms of the adrenoceptors, which are diffusely present in the general population and may be the basis of inter-individual differences in the response to therapeutic β1AR agonists and antagonists in cardiovascular and other diseases.\textsuperscript{57–69}

Zaroff and colleagues\textsuperscript{70} found a correlation between specific β- and α-adrenoceptor polymorphisms and an increased release and sensitivity to catecholamines in patients with SAH and related cardiac involvement. Single adrenoceptor polymorphisms were associated with a three- to five-fold increase in the risk of cardiac dysfunction, whereas patients with combinations of two of these polymorphisms had a 10- to 15-fold increased risk of cardiac injury after SAH.\textsuperscript{70}

Other investigators,\textsuperscript{71} instead, excluded a correlation between adrenergic polymorphisms and Takotsubo cardiomyopathy. However, familial cases of Takotsubo syndrome have been described, suggesting a genetic predisposition towards this syndrome.\textsuperscript{72, 73} Recently, in patients with LV apical ballooning syndrome, a correlation was found with a polymorphism of G protein-coupled receptor kinase 5 (GRK5), a protein involved in post-receptor signal transduction.\textsuperscript{74}

Clinical research directed to the detection of genetic causes of sympathetic nervous system overactivity could help in the identification and stratification of patients at risk of NSC and in the exploration of potential cardio-protective benefits of adrenergic block in subgroups of patients who are genetically more susceptible to the effects of these drugs.

**Monitoring for NSC**

Participants at the Neurocritical Care Society consensus conference on the management of SAH patients agreed that a baseline assessment of cardiac function with serial enzymes, ECG, and echocardiography may be beneficial, especially if any sign of myocardial dysfunction is present and that cardiac output should be monitored in those patients with myocardial dysfunction or haemodynamic instability,\textsuperscript{75} even though no data are available to demonstrate an effect on outcomes.

Although cardiac abnormalities have been described most frequently after SAH, this complication should always be suspected whenever ECG abnormalities or myocardial dysfunction occur suddenly or unexpectedly after any acute severe cerebral event. Physicians should also be alerted to this diagnosis in patients who require aneurysm clipping or coiling; data indicate that there is no significant difference in cardiac morbidity between surgical and endovascular treatments.\textsuperscript{11–76} The possible occurrence of NSC at any time in the perioperative period should be considered, because it may affect maintenance of systemic and brain homeostasis, and determine secondary brain damage (Fig. 1).

All SAH patients should be screened on admission with a full cardiac evaluation including a complete clinical history, a 12-lead ECG, a chest X-ray, cardiac enzyme profile, pro-BNP level, lipid profile, and electrolyte panel.\textsuperscript{11} If the ECG is abnormal or troponin I levels are elevated, transthoracic echocardiography needs to be performed to evaluate the impact of wall motion abnormalities on haemodynamic status and the response to treatment and, after 5–7 days, to document the reversibility of the syndrome. Because recent studies suggest that coronary flow reserve is temporarily impaired in the acute phase of Takotsubo cardiomyopathy, assessment of coronary flow by transthoracic Doppler echocardiography may be helpful.\textsuperscript{77} Troponin I is a highly sensitive and specific marker of myocardial dysfunction in SAH and is predictive of an increased risk of hypotension, pulmonary oedema, LV systolic dysfunction, and delayed cerebral ischaemia from vasospasm.\textsuperscript{78} Relatively limited troponin release relative to the magnitude of LV dysfunction has been described, and it has been proposed that an ejection fraction of <40\% and troponin I <2.8 ng ml\textsuperscript{-1} are predictive of NSC rather than acute myocardial infarction.\textsuperscript{79}

Elevated BNP levels also occur after SAH, with a described trend towards higher BNP levels in patients with an admission Hunt–Hess grade of 3–5 (449 pg ml\textsuperscript{-1}) vs grade 1–2 patients (189 pg ml\textsuperscript{-1}).\textsuperscript{80} The detection of a two- to three-fold increase in BNP levels in plasma but not in cerebrospinal fluid supports the heart as the source of increased BNP levels after SAH.\textsuperscript{81} Norepinephrine may cause an increase in the load on the cardiac ventricles, which may stimulate BNP secretion, which in turn
causes hyponatraemia, potentially leading to symptomatic vasospasm because of volume depletion.\textsuperscript{82}

In patients identified to be at higher risk of developing NSC (high Hunt and Hess score, documented insular involvement on neuroimaging, or the presence of comorbidities that may further jeopardize clinical management), more careful monitoring of cardiovascular function should be planned, in terms of serial ECGs and monitoring of pro-BNP and troponin levels. In the case of cardiogenic shock requiring vasoactive drugs, invasive haemodynamic monitoring should be considered. In the case of wall motion abnormalities in a single vascular territory and clinical presentation non-concordant with features of NSC, cardiac catheterization should be considered.\textsuperscript{31,12,0} Indexes of sympathetic activity that can be used in the evaluation of neurocardiogenic injury are listed in Table 1. Cardiac magnetic resonance imaging using a delayed enhancement technique may also help in differentiating stress cardiomyopathy from acute myocardial infarction or death.\textsuperscript{92} In SAH patients, power spectral analysis of HRV showed enhanced vagal activity in the acute phase of the disease, probably secondary to high intracranial pressure, explained as accentuated antagonism after high catecholamine concentrations.\textsuperscript{93} In a study evaluating the differential effects of stroke localization on ANS, lesions that involved the right insula had the lowest standard deviation of normal R–R intervals, LF, and HF amplitudes, further supporting the hypothesis that the insula (especially the right insula) may be an important anatomic location in the control of autonomic tone.\textsuperscript{94}

### The role of heart-rate variability in NSC

Given the central role of the ANS in the genesis of cardiac abnormalities after SAH or stroke, a better elucidation of ANS dysfunction in the acute phase of the disease could help in identifying at-risk patients. Heart-rate variability (HRV), a noninvasive tool that reflects the balance of the ANS regulation of the heart rate, may detect the presence of autonomic neuropathy complicating acute brain injury.\textsuperscript{88}

There is increasing interest in the study of HRV in anaesthesia and critical care, to investigate the effects of anaesthetics on the ANS, and the prognostic role of HRV in the critical illness.\textsuperscript{38,89} One of the new findings is that HRV is important not only for what it tells us about the state of the heart, but also for what it tells us about the state of the brain.\textsuperscript{90}

### Table 1 Indexes of sympathetic activity

<table>
<thead>
<tr>
<th>Sympathetic Activity</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Tissue, plasma and urine catecholamine levels</strong></td>
<td>The levels of catecholamines (noradrenaline, adrenaline) in the tissue, plasma, and urine. This can be used to assess sympathetic activity.</td>
</tr>
<tr>
<td><strong>Heart-rate variability</strong></td>
<td>Represents the beat-to-beat oscillation of heart rate. Power spectral analysis of a sequence of 500 R–R intervals can detect two major bands: LF is the expression of baroreceptor-mediated regulation and occurs because of the contribution of parasympathetic and mainly sympathetic discharge, and HF reflects the modulation of vagus nerve discharge caused by respiration.</td>
</tr>
<tr>
<td><strong>Baroreflex sensitivity</strong></td>
<td>A measure of the reflex response (both vagal and sympathetic) to the stimulation of the baroreceptors induced by arterial pressure changes. It can be measured by infusion of vasoactive drugs or non-invasively through spontaneous variations in arterial pressure and R–R intervals.</td>
</tr>
<tr>
<td><strong>Cardiac MIBG scintigraphy</strong></td>
<td>Detection of the uptake of a specific tracer showing the activity of sympathetic post-synaptic fibres. MIBG bears a structural resemblance to norepinephrine, and the uptake of MIBG in various tissues closely parallels that of norepinephrine. MIBG is used to assess human cardiac sympathetic nervous viability and function.</td>
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<tr>
<td><strong>Microneurography MNSA, SSA, RNSA</strong></td>
<td>(muscle, skin, and renal sympathetic nerve activity): Direct recording of the activity of the vasoconstrictive sympathetic fibres at muscle, skin, and renal levels.</td>
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Standard HRV measurements have been widely accepted.\textsuperscript{91} Frequency domain techniques using the fast Fourier transform method applied to 5 min recordings determine a spectrum with two major bands of frequency: low frequency (LF) is the expression of baroreceptor-mediated regulation from parasympathetic and mainly sympathetic discharge, and high frequency (HF) reflects the modulation of vagus nerve discharge caused by respiration; longer-term recordings also enable ultra-LF to be assessed. The LF/HF ratio reflects sympathovagal balance. Several factors may affect HRV measurement, including temperature, volaemic status, ventilatory settings, sedation, medications, and manoeuvres that stress the ANS: all these factors should be considered when interpreting results.\textsuperscript{88}

In neurosurgically critically ill patients, it has been reported that a reduction in the total power variability of the R–R interval and a lowered LF/HF ratio are associated with poor-quality recovery or death.\textsuperscript{92} In SAH patients, power spectral analysis of HRV showed enhanced vagal activity in the acute phase of the disease, probably secondary to high intracranial pressure, explained as accentuated antagonism after high catecholamine concentrations.\textsuperscript{93} In a study evaluating the differential effects of stroke localization on ANS, lesions that involved the right insula had the lowest standard deviation of normal R–R intervals, LF, and HF amplitudes, further supporting the hypothesis that the insula (especially the right insula) may be an important anatomic location in the control of autonomic tone.\textsuperscript{94}

Hence, a combined HRV and functional magnetic resonance imaging approach to the study of acute brain injury patients could provide important prognostic information, helping intensivists to identify high-risk patients who require more intensive monitoring to prevent sudden death.\textsuperscript{94}

Furthermore, it has been shown that LF%, HF/HF, and Hunt–Hess scale are significant independent predictors of in-hospital mortality in SAH patients.\textsuperscript{95}

The importance of HRV as a marker of stress has been recently highlighted, and the possibility of a functional link between the brain and the heart studied. In particular, neuroimaging studies have suggested associations between HRV and specific brain regions including the amygdala and ventromedial prefrontal cortex, thus further supporting a structural and functional link between the brain and the heart.\textsuperscript{90}
Although catecholamine-induced acute myocardial stunning represents the main expression of the interconnection between the brain and the heart, the occurrence of secondary brain damage as a consequence of myocardial stunning is an expression of the heart in turn ‘talking’ to the brain. Bilateral signalling involving arterial baroreflexes represents another expression of the strict bidirectional connections between the two organs. With the aim of maintaining an adequate cerebral blood flow, baroreceptors send afferent signals to the brain, which in turn sends efferent outputs to regulate changes in arterial pressure.90

**Proposed treatment for NSC**

Although usually transient and reversible and, thus, requiring only supportive treatment, the clinical course of NCS can be severe, with hypokinesis, akenis, or dyskinesis of the left ventricle and can be detrimental, especially if occurring in the acute phase of an acute brain injury, when maintenance of systemic homeostasis is mandatory to reduce secondary brain injury.

Haemodynamic instability, arrhythmias, cardiogenic shock, pulmonary oedema, and sudden cardiac death are the main concerns in the management of these patients in the neuro ICU and in the perioperative setting, because these complications occur more frequently than previously suspected.3 20 The clinical presentation may be similar to an acute myocardial infarct and the ejection fraction may decrease significantly. LV dysfunction with impaired haemodynamics and possible embolization from LV mural thrombus formation in those with apical involvement may jeopardize cerebral blood flow and induce ischaemic brain damage. Dynamic LV outflow tract obstruction may be evident when a small LV becomes hypercontractile, especially in the basal segments.96

The discussed pathophysiological hypotheses may guide the management of these patients during acute myocardial stunning. The evidence of supraphysiologic levels of plasma catecholamines31 33 30 and the increased sympathetic activity provide strong physiological support for the use of β-blockers.97 These drugs are an important component of the treatment regimen for chronic heart failure and exert a protective effect in cerebrovascular disease, acting by a membrane stabilizing and antioxidant effect, by block of sodium and calcium channels, and by decreasing tumour necrosis factor (TNF)-α levels, among other mechanisms.97 In a large prospective study in stroke patients, β-blocker use was associated with less severe stroke on presentation, correlated with lower cardiac sympathovagal tone, and exerted its protective effect through sympatholytic action, inhibition of thrombin generation, and reduced inflammation.97 Furthermore, β-antagonists may protect cardiac myocytes from norepinephrine-stimulated apoptosis.98

Recently, landiolol, an ultra-short acting, highly selective β1-receptor antagonist was investigated in patients with SAH undergoing intracranial aneurysm surgery. Intraoperative administration of landiolol significantly reduced heart rate without affecting arterial pressure. No significant differences were detected in interleukin-6 and interleukin-1ra values in the landiolol vs control group and there were no differences in myocardial ischaemia or delayed neuronal deficits, possibly because of the limited number of patients and the restricted time window of drug administration.99

In the case of emergency surgery for SAH patients, the occurrence of myocardial stunning may affect the timing of surgery and be responsible for an increased risk of perioperative cardiovascular deterioration. Decreased myocardial function and haemodynamic instability, associated with hypertension and decreased oxygenation, can be devastating during periods of cerebral vasospasm.

Although the topic is controversial, neurogenic stunned myocardium may benefit from inotropic medication to maintain an equilibrium between myocardial oxygen supply and demand. Epinephrine-mediated stunning is recognized as a causative factor for NSC, so that administration of epinephrine may worsen negative inotropism further increasing the switch from GS protein signalling to Gi protein signalling.24 Caution is advised when using sympathomimetic drugs in patients with Takotsubo cardiomyopathy, because their effects may be less predictable because of the dysfunctional myocardial response to catecholamine stimulation.100 Levosimendan, a non-catecholamine inotrope, is a novel calcium sensitizer, which is used to improve myocardial contractility by stabilizing troponin C and enhancing the calcium sensitivity of cardiac myofilaments in heart failure patients. Not only does it increase myocardial systolic performance, but it also improves coronary perfusion, has an anti-apoptotic and anti-stunning effect, and has been reported to be successful in limited case series of Takotsubo cardiomyopathy. Levosimendan theoretically may be the inotrope of choice in Takotsubo cardiomyopathy-related shock.101

In limited cases of life-threatening acute LV failure, intra-aortic balloon pump and ventricular assist devices may also be necessary.20 24

In addition to elevated catecholamines, the role of oestradiol in the pathogenesis of NSC has recently been investigated, with the hypothesis that lack of oestradiol in post-menopausal women may predispose them to develop LV abnormalities after SAH.102 In a retrospective analysis, SAH grading, increased plasma norepinephrine, and decreased plasma oestradiol levels were independently associated with wall motion abnormalities. Based on these results, the administration of oestradiol to post-menopausal female patients with SAH complicated by severe wall motion abnormalities could be considered a possible therapeutic option.102

Although rare, the eventuality of LV mural thrombus formation in the case of apex involvement, with possible systemic thromboembolism, should be considered and prevented by anti-coagulation if not contraindicated.103

The effect of sympathetic storm should be considered also in potential organ donors who may become eligible to donation after early and aggressive hormonal treatment with insulin, methylprednisolone, vasopressin, and T3, allowing them to recover from NSC.104

Whether treatments are available that can induce cardioprotection and hence improve clinical outcomes after SAH is still unknown and needs to be tested in clinical trials.105
Takotsubo cardiomyopathy in the perioperative period

Takotsubo is a particular form of stress-related cardiomyopathy syndrome mimicking an acute coronary event and presenting with transient LV wall motion abnormalities characterized by apical and mid-ventricular akinesis compensated for by basal hyper-kinesis extending beyond a single epicardial coronary territory of distribution, markedly prolonged S-T segment and arrhythmias, S-T segment elevation, T-wave inversion, or all.20

As previously stated, this syndrome shares common pathophysiological mechanisms with NSC. The depressed contractile function during Takotsubo was attributed by Lyon and colleagues26 to a switch, induced by high levels of epinephrine, in β2-receptor signalling from Gs protein to Gi proteins with depression of contractility mainly in the apex region where β-adrenoceptor density is higher. β stimulation through cyclic adenosine monophosphate (cAMP) increase and the resultant increased intracellular level of calcium and reactive oxygen species leads to myocardocyte apoptosis through opening of the mitochondrial permeability transition pore; in Takotsubo, however, as illustrated in Fig. 4, the aforementioned opening of the mitochondrial permeability transition pore; in Takotsubo cardiomyopathy, 118 but its use in this setting has been described because of anaphylaxis, meperidine-induced histamine release,110 transfection reaction as a result of histamine release, activation of the so-called histamine-adrenergic crosstalk,111 and the infusion of adrenergic drugs.

Regional anaesthesia reduces sympathetic nervous stimulation arising from local stimulation and catecholamine release and provides optimal postoperative pain control; nevertheless, Takotsubo syndrome has also been described during spinal anaesthesia.109 During the perioperative period, Takotsubo has also been described because of anaphylaxis, meperidine-induced histamine release,110 transfection reaction as a result of histamine release, activation of the so-called histamine-adrenergic crosstalk,111 and the infusion of adrenergic drugs.

Regional anaesthesia reduces sympathetic nervous stimulation arising from local stimulation and catecholamine release and provides optimal postoperative pain control; nevertheless, Takotsubo syndrome has also been described during spinal anaesthesia.108 109

Can we prevent the occurrence of Takotsubo during the perioperative period?

Although there is no consensus regarding the anaesthetic management of these patients,112 117 it is crucial that any potential triggering event that could result in a catecholamine surge and consequent cardiac dysfunction be avoided during the entire perioperative period. Brief laryngoscopy, smooth emergence, and extubation are important to avoid increases in catecholamine release, which may trigger the syndrome.112

Although regional anaesthesia may reduce circulating catecholamines associated with surgical stress, it does not completely protect against it, as an awake patient is potentially more susceptible to psychological stress, thus triggering the cardiomyopathy,112 and association of adequate sedation may, therefore, be helpful.

A deep level of anxiolysis in the preoperative period, an adequate level of anaesthesia before any intense stimulation, and an optimal postoperative analgesia may help reduce the development of Takotsubo, by limiting the risk of elevated perioperative endogenous catecholamine levels.

It can be argued that opioids and the central α2-inhibitor, dexmedetomidine, both of which target the locus coeruleus, the important supraspinal sympathetic centre that regulates the reflex response to stress, may be the most appropriate drugs currently available to prevent the occurrence of Takotsubo.118 119 Indeed, it has been demonstrated that the stimulatory effect of dexmedetomidine on the central α2-receptors (provided with a modulatory role of sympathetic activity) may protect against psychological stress and anxiety and can reduce conditioned fear from prior unpleasant experiences acting on the amygdala and also improving haemodynamic stability.120 121 Dexmedetomidine may also protect against psychological stress by depressing the activity of the amygdala related to anxiety.120

As already discussed, treatment of stress-related cardiomyopathy syndromes may vary from mainly supportive care to more aggressive treatments. The perioperative use of β-blockers is highly recommended. Short-term anti-coagulation is recommended to prevent apical mural thrombus. Magnesium, which is known to be involved in several fundamental processes including gating of calcium channels, regulation of adenylate cyclase, cardiac excitability, control of vasomotor tone, and neurotransmitter release,122 has also been proposed as a potential drug to attenuate the stress response related to Takotsubo cardiomyopathy, but its use in this setting needs to be evaluated. Because stress can trigger myocardial stunning, stress-coping strategies and limiting exposure to stressful environments or triggers may also help to reduce negative emotional responses.23

Experimental models of immobilization stress have been used to induce intense sympathetic-adrenal activation reproducing stress cardiomyopathy124 and demonstrating that the observed physiological and molecular alterations are prevented by pre-treatment with αβ-blockers. Furthermore, α and βAR block attenuated immobilization-induced upregulation of heme oxygenase-1 mRNA levels, supporting a role for

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oxidative stress cardiomyopathy and suggesting a role for anti-
oxidative stress agents in its treatment. Vigilance and a high index of suspicion are essential to avoid misdiagnosis or delayed recognition, and the entire surgical team should be educated in the recognition of this potentially life-threatening syndrome. Establishment of a Registry of peri-
operative Takotsubo cases may play an important role in identifying the real scale of the problem, understanding the role played by different mechanisms in individual cases, and establishing the most suitable corrective measures to prevent its onset.

In cases of Takotsubo cardiomyopathy occurring before elective surgery, it is reasonable to delay surgery until myocardial wall motion abnormalities return to normal.

**Conclusions**

Intense brain–heart crosstalk is increasingly recognized in the acute phase after severe brain injury, NSC being the best-known clinical life-threatening expression.

Recent research has focused on how to identify, at an early stage, patients at risk of developing NCS after acute brain injury and how to protect them. Adequate screening and monitoring of cardiovascular function should be considered at the time of admission of these patients, and careful re-evaluation planned accordingly.

The relationship between NSC and brain anatomy, as studied with neuroimaging techniques, should be investigated to elucidate whether vulnerability to NSC is predicted by...
regional differences in affected regions of the brain. The impact of cardiac dysfunction on brain homeostasis should be considered for the possible role of NSC as a deleterious secondary insult to the brain. What still needs to be addressed in future research is whether detectable patient-specific factors may help explain different susceptibilities to the disease, so that these factors can be promptly detected and adverse events anticipated. A more complete understanding of the pathogenesis of the syndrome requires further research. Vigilance and a high index of suspicion are critical to a prompt diagnosis of stress-related cardiomyopathy syndromes occurring during anaesthesia and throughout the perioperative period.

**Authors’ contributions**
A.T.M.: organizing and writing the paper and paper revision; A.M. and A.S.: literature search and manuscript preparation; L.M.: manuscript revision; L.S.: manuscript revision and manuscript preparation.

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**Declaration of interest**
None declared.

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**References**
2. Samuels MA. The brain-heart connection. *Circulation* 2007; **116**: 77 – 84
27. Masuda T. Systolic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. *Stroke* 2002; **33**: 1671 – 6
85 Iltumur K, Tamam Y, Karahan Z, Guzel A, Altindag R. Coexisting et al.

89 Laitio T, Jalonen J, Kuusela T, Scheinin H. The role of heart rate vari-

88 Mazzeo AT, La Monaca E, Di Leo R, Vita G, Santamaria LB. Heart rate

et al.


83 Beard EF, Robertson JW, Robertson RC. Spontaneous subarach-

et al.


75 Diringer MN, Bleck TP, Claude Hemphill J III, et al.

73 Kumar G, Holmes DR Jr, Prasad A. ‘Familial’ apical ballooning syn-

drome (Takotsubo cardiomyopathy). Int J Cardiol 2010; 144: 444–5

74 Spinnelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimal-

caro B. L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syn-

76 Miss JC, Kopelnik A, Fisher LA, et al. Cardiac injury after subarach-
noid hemorrhage is independent of the type of aneurysm therapy. Neu-
rosurgery 2004; 55: 1244–50; discussion 50–1


78 Naidech AM. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. Circulation 2005; 112: 2851–6


81 Espiner EA, Leikis R, Ferch RD, et al. The neuro-cardio-endocrine re-


82 Tomida M, Muraki M, Uemura K, Yamazaki K. Plasma concentra-


83 Beard EF, Robertson JW, Robertson RC. Spontaneous subarach-

84 Yamanaka O, Fujiwara Y, Nakamura T, et al. [A case of subarach-
noid hemorrhage with sick sinus and advanced AV block.] Kokyu To Junkan 1992; 40: 715–9


87 Bhattacharya IS, Sandeman D, Dweck M, McKie S, Francis M. Electro-

cardiographic abnormalities in a patient with subarachnoid haemorrhage. BMJ Case Rep 2011; doi: 10.1136/bcr.08.2010.3253

88 Mazzeo AT, La Monaca E, Di Leo R, Vita G, Santamaria LB. Heart rate variability: a diagnostic and prognostic tool in anesthesia and in-

89 Laitio T, Jalonen J, Kuusela T, Scheinin H. The role of heart rate vari-

ability in risk stratification for adverse postoperative cardiac events. Anesth Analg 2007; 105: 1548–60

90 Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-


97 Laowattana S, Oppenheimer SM. Protective effects of beta-


98 Communal C, Singh K, Pimentel DR, Colucci WS. Norepinephrine stim-


siologist 2010; 22: 230–9


101 Padyachee L. Levosimendan: the inotrope of choice in cardio-

genic shock secondary to Takotsubo cardiomyopathy?. Heart Lung Circ 2007; 16 (Suppl. 3): S65–70

102 Sugimoto K, Inamasu J, Hirose Y, et al. The role of norepinephrine and estradiol in the pathogenesis of cardiac wall motion abnor-

mality associated with subarachnoid hemorrhage. Stroke 2012; 43: 1897–903

103 Jabiri MZ, Mazighi M, Meimoun P, Amarenco P. Tako-tsubo syn-


105 Okabe T, Kanzoria M, Rincon F, Kraft WK. Cardiovascular protection to improve clinical outcomes after subarachnoid hemorrhage: is there a proven role?. Neurocrit Care 2013; 18: 271–84

106 Neff HM, Mollmann H, Hilpert P, et al. Activated cell survival cascade protects cardiomyocytes from cell death in Tako-Tsubo cardiomy-
opathy. Eur J Heart Fail 2009; 11: 758–64


108 Jaboudon M, Bonnin M, Bolandard F, Chansaume S, Dauphin C, Bazin JE. Takotsubo syndrome during induction of general anaes-


111 Zhou JQ, Choe E, Ang L, et al. Stress-induced cardiomyopathy associated with a transfusion reaction: a case of potential
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