Cardiovascular complications of brain injury

Revalidation FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 3E05

Tamsin Gregory MBBS MRCP FRCA
Martin Smith MBBS FRCA FFICM

Key points

Cardiovascular complications are common after brain injury and are associated with increased mortality and morbidity.

Neurogenic cardiac injury is related to brain injury-induced catecholamine and inflammatory responses.

The neurogenic stunned myocardium (NSM) syndrome is caused by local release of norepinephrine from myocardial sympathetic nerve terminals.

The NSM syndrome is characterized by ECG changes, cardiac arrhythmias, release of biomarkers of cardiac injury, and left ventricular dysfunction

Neurogenic cardiac abnormalities are often transient and management should focus on general supportive care and treatment of the injured brain.

Tamsin Gregory MBBS MRCP FRCA
Clinical Fellow
Department of Neurocritical Care
The National Hospital for Neurology and Neurosurgery
University College London Hospitals
Queen Square
London WC1N 3BG
UK

Martin Smith MBBS FRCA FFICM
Consultant and Honorary Professor
Department of Neurocritical Care
The National Hospital for Neurology and Neurosurgery
University College London Hospitals
Box 30
Queen Square
London WC1N 3BG
UK
Tel: +44 20 3448 4711
E-mail: martin.smith@uclh.nhs.uk
(for correspondence)

Cardiovascular complications are common after brain injury and associated with increased morbidity and mortality.[1,2] The spectrum of abnormalities includes hypertension, hypotension, ECG changes, cardiac arrhythmias, release of biomarkers of cardiac injury, and left ventricular (LV) dysfunction. The abnormalities are usually reversible and management should therefore focus on general supportive care and on treatment of the underlying brain injury.

Pathophysiology

Neurogenic cardiac injury is related to brain injury-induced catecholamine and neuroinflammatory responses,[3] and is more likely in those with the most severe neurological insult.

Catecholamine effects

Traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) induce a systemic catecholamine 'storm' driven by the central neuroendocrine axis which massively increases sympathetic outflow and activates the adrenal glands. Damage to the insular and hypothalamus also initiates a complex cascade of events, including activation followed by dysfunction of the autonomic nervous systems and an intense inflammatory response, which have major adverse effects on the heart (Fig. 1).[4] High sympathetic tone persists for some time after brain injury, with circulating catecholamine levels remaining high for up to 10 days. This is potentially a protective mechanism designed to maintain cerebral perfusion in the presence of raised intracranial pressure (ICP), but it also has several adverse effects.

Systemic circulatory effects

The intense systemic vasoconstriction associated with the catecholamine 'storm' increases cardiac afterload, myocardial workload, and oxygen demand. Because of simultaneous coronary vasoconstriction, the increase in myocardial oxygen demand is not associated with an increase in oxygen delivery and subendocardial ischaemia and impaired ventricular function may follow. This can lead to cardiogenic pulmonary oedema and systemic hypotension.[4] Hypotension may also occur because of head injury-related disruption of brain stem centres for haemodynamic control, commonly related to diffuse axonal injury. Although neurogenic hypotension is uncommon after isolated head injury in adults, it is associated with higher mortality than haemorrhagic hypotension.

Neurogenic stunned myocardium syndrome

The neurogenic stunned myocardium (NSM) syndrome is a reversible neurologically mediated cardiac injury characterized by ECG changes, arrhythmias, LV dysfunction, and release of biomarkers of cardiac injury. It was previously assumed to be related to covert coronary artery disease or myocardial ischaemia secondary to systemic, catecholamine-induced hypertension and tachycardia, but animal and human studies have confirmed that NSM is caused by excessive norepinephrine release from myocardial sympathetic nerve terminals and is independent of plasma catecholamine levels.[4] The release of catecholamines into the myocardial interstitium leads to prolonged opening of β1-adrenergic receptor-controlled calcium channels and rapid depletion of adenosine triphosphate. This results in mitochondrial dysfunction and cell death and is associated with a classic histological picture called myocardial contraction band necrosis that is characterized by focal myocytolysis, myofibrillar degeneration, and irregular cross-band formation. The histological changes are most dense in subendocardial regions of the heart, with relative apical sparing, corresponding with areas of sympathetic innervation rather than specific vascular territories.

doi:10.1093/bjaceaccp/mkr058

The severity of NSM and hence the degree of myocardial damage is related to the severity of the underlying brain injury.[5] Although most commonly associated with SAH, NSM is seen after other types of brain injury and also in non-neurological conditions such as phaeochromocytoma, near drowning, and severe emotional stress.[6] It develops soon after the neurological insult and, in animal models, there is evidence of cardiac myocyte damage within 4 h of SAH.

Neuroinflammation

TBI and SAH also activate an intense neuroinflammatory response that leads to the release of immunologically active mediators, including cytokines, adhesion molecules, and other multifunctional peptides, from the brain into the systemic circulation. This initiates a systemic inflammatory response syndrome that is an important cause of systemic organ system dysfunction and failure after brain injury. Such changes have been implicated in the pathogenesis of ventricular arrhythmias after SAH.[7] There is a complex interaction between the brain and the immune and autonomic nervous systems (Fig. 1).[3,4] It appears that parasympathetic dysfunction, and activation of the sympathetic nervous system, also plays a role in cardiac damage via modulation of the myocardial inflammatory response through acetylcholine receptors. This leads to myocardial dysfunction and cell death because of unchecked myocardial inflammation.[4]

Clinical features, diagnosis, and management

In many cases, brain injury-related cardiovascular dysfunction resolves spontaneously, emphasizing the importance of proactive management, including treatment of the underlying brain injury, and general supportive critical care.

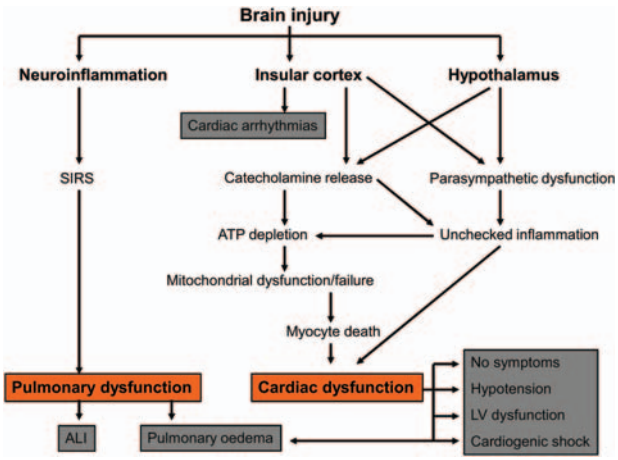

Fig 1 The pathophysiology of cardiovascular complications after brain injury. SIRS, systemic inflammatory syndrome; ATP, adenosine triphosphate; ALI, acute lung injury.

Cardiovascular complications

Neurogenic cardiovascular dysfunction may cause minimal clinical effects but, in severe cases, can lead to cardiogenic shock and pulmonary oedema.

Arterial pressure

The initial catecholamine surge results in hypertension and tachycardia, and early studies demonstrated that β-adrenergic blockade reduces myocardial injury and improves neurological outcome after SAH. Although sympathetic blockade is generally considered to be impractical because of its potential adverse effects on arterial pressure and cerebral perfusion pressure (CPP), retrospective studies have demonstrated mortality benefits after TBI in patients pre-exposed to β-blockers. The potential benefits are likely to include cardioprotection in patients with NSM through limitation of myocardial oxygen demand by reduction in heart rate, stroke volume, and arterial pressure, and (speculative) direct neuroprotective effects through modulation of cerebral blood flow and metabolism. Although it remains to be established whether post-injury β-blockade produces similar beneficial effects to pre-exposure, a recent meta-analysis found that bradycardia is associated with a decreased risk of death after SAH.[1] Other sympatholytic therapies, such as magnesium sulphate and clonidine, have been investigated, but there is no clinical evidence to support their use after brain injury.

As the catecholamine surge subsides, the initial hyperdynamic response is often followed by significant hypotension because of unopposed peripheral vasodilatation and ventricular dysfunction. Arterial pressure usually responds to fluid resuscitation and standard vasopressor/inotropic support. Norepinephrine is widely used and provides predictable control of arterial pressure and CPP after TBI. Vasopressin may be effective in refractory hypotension but is associated with cerebral vasoconstriction and a risk of brain ischaemia so should be used with caution. Dobutamine is effective in normalizing cardiac index in NSM-related low cardiac output states after SAH.

ECG morphological changes

Brain injury-related ECG abnormalities have been recognized for more than five decades and are particularly common after SAH where they are reported in 49–100% of cases. The most common findings are ST segment changes, flat or inverted T waves, prominent U waves, and prolongation of the QTc interval (QTc is the QT interval corrected for heart rate).[8] Clinical studies show no correlation between circulating catecholamine levels and ECG abnormalities, suggesting that they are also due to myocardial injury secondary to local sympathetic activation. Although it is well established that neurogenic ECG changes are not related to cardiac hypoperfusion, it can nevertheless be difficult to differentiate them from an acute ischaemic coronary event (Fig. 2). ECG changes occur most commonly in the first few days after injury and are often transient because repolarization normalizes as the

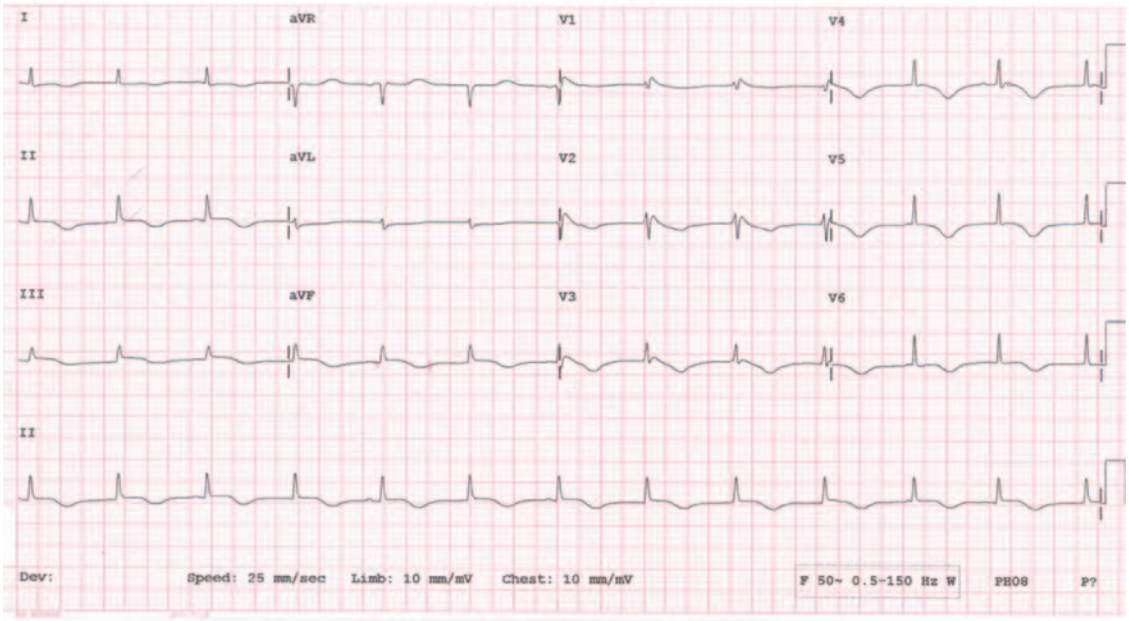

Fig 2 Typical ECG changes after SAH showing deep T wave inversion and prolongation of the QTc interval.

neurological insult resolves. They may, however, persist for up to 8 weeks in some cases. Neurogenic ECG changes are generally asymptomatic, but abnormalities such as ST segment depression and abnormal T waves can be associated with the development of a delayed ischaemic neurological deficit, poor outcome, and death after SAH. Excessive prolongation of the QTc interval may be a cause of sudden cardiac death after brain injury. It is of note that QTc interval prolongation persists in patients with an unfavourable outcome after SAH but improves in those who have a good outcome.

Cardiac arrhythmias

Cardiac rhythm disturbances, including sinus tachycardia, atrial fibrillation, premature atrial and ventricular contractions, and AV dissociation, are also common after brain injury and usually occur within the first 7 days.[8] The incidence of new arrhythmias after acute ischaemic stroke is around 25%, compared with only 3% in an age-matched control group. Severe rhythm disturbances, such as torsades de pointes and ventricular fibrillation, are rare and often associated with elevated biomarkers of cardiac injury. Most neurogenic arrhythmias are benign, but others carry a poor prognosis. They have been described in 35% of patients after SAH but only 5–8% are life-threatening.[9] However, the true incidence of malignant arrythmias is uncertain because they may be the cause of prehospital mortality in some patients. The exact mechanism of sudden cardiac death after brain injury is unclear, but severe QTc prolongation, driven by abnormalities in the insula, is thought to be responsible. Drugs that prolong the QTc interval should therefore be avoided after brain injury, even into the rehabilitation phase.

A 12-lead ECG should be recorded on admission and repeated at 24 h intervals until any abnormalities have resolved. There is no specific treatment for brain injury-induced cardiac arrhythmias, and although standard therapies such as correction of electrolyte disturbances should be provided, management of the underlying intracranial pathology is the most effective way to prevent and treat the arrhythmia. Significant ECG abnormalities, particularly those associated with ventricular dysfunction, may require specific intervention because of the risk of progression to a malignant rhythm pattern.

Propofol infusion syndrome

The propofol infusion syndrome (PRIS) is characterized by unexplained metabolic acidosis, elevated creatinine kinase, rhabdomyolysis, and widespread ECG changes and can lead to cardiac myocytolysis, rhabdomyolysis, and acute renal failure.[10] It is more common after high-dose or long-term propofol infusion but can also occur as an idiosyncratic response. The exact aetiology is unclear, but impaired utilization of fatty acids within the mitochondria is a likely cause.

Propofol is widely used to sedate brain-injured patients and to control ICP, and the ECG consequences of PRIS can be difficult to differentiate from those associated with the NSM syndrome. It is recommended that a propofol infusion rate of 4 mg kg^{-1} h^{-1} should not be exceeded in order to minimize the risk of PRIS. Propofol infusion should be discontinued immediately if PRIS is suspected and attempts made to exclude NSM as a differential or coincidental diagnosis in brain-injured patients.

Biomarkers of cardiac injury

Elevation of cardiac troponin I (cTnI) has been reported in 20–68% of patients after SAH (mean incidence 36%) and usually peaks within 24–36 h.[9] cTnI is more sensitive than creatine phosphokinase-myocardial fraction (CK-MB) for detection of LV dysfunction, being 100% sensitive and 86% specific compared with 29 and 100%, respectively, for CK-MB.[11] The peak concentration is usually below the threshold for the diagnosis of myocardial infarction but may be associated with a mild, transient impairment of ventricular function in 50% of patients. The degree of cTnI increase is related to the severity of the initial brain injury and a highly positive response is an independent predictor of acute regional wall motion abnormalities (RWMAs) and associated with an increased risk of death and poor functional outcome in survivors.[5] There is a higher rate of NSM-related cardiac damage in females, suggesting that sex differences affect the vulnerability of the heart to catecholamines after brain injury.[6]

Elevated serum B-type natriuretic peptide (BNP) is also independently associated with LV dysfunction, pulmonary oedema, and adverse neurological outcomes after SAH.[12]

Ventricular dysfunction

Impaired LV contractility, hypokinesia, and low ejection fractions are associated with the NSM syndrome. There is a characteristic pattern of RWMAs involving the basal and middle portions of the anteroseptal and anterior ventricular walls, with relative apical sparing (Fig. 3).[13] This reflects the distribution of sympathetic nerves rather than specific vascular territories in line with the known aetiology of NSM. LV dysfunction occurs in around 15% of patients after SAH, usually within 3 days of the ictus, but the degree of dysfunction is often mild. In one study, mean LV ejection fraction was <50% in only 8% of patients.[13] Although LV dysfunction is usually temporary, it is associated with higher mortality after SAH. Diastolic dysfunction is much more common than previously believed and, in one study, was identified in 71% of patients after SAH and associated with a higher incidence of pulmonary oedema.[14]

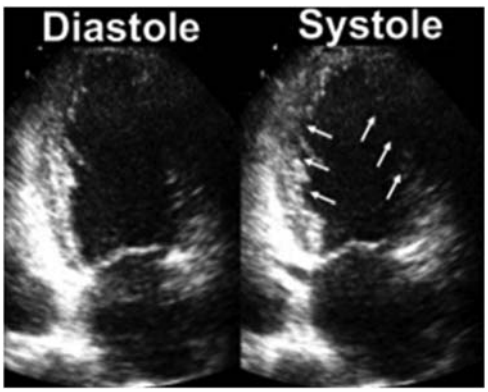

Fig 3 Echocardiogram of a patient with Hunt and Hess grade 3 SAH showing midventricular wall motion abnormalities (arrows) in the apical two-chamber view. Wall motion score was 1.9 and ejection fraction 30%. (modified from Tanabe and colleagues, *Am J Cardiol* 2008; **102**: 1545–50, with permission).

Takotsubo cardiomyopathy, also referred to as left apical ballooning or 'broken heart' syndrome, is a transient, virtually global LV dysfunction that is characterized by apical and mid-ventricular akinesia and relative sparing of the basal segment.[15] It is a well-recognized response to sudden physical or emotional stress and generally has a benign prognosis. Takotsubo cardiomyopathy is a rare cause of ventricular dysfunction after SAH but is associated with increased mortality in this context.

Differentiating between neurogenic and coronary events

Coronary angiography is the definitive diagnostic test to exclude coronary artery disease but is seldom indicated in this high-risk group of patients.[4] In any case, the presence of significant coronary artery disease does not exclude co-incidental NSM. Brain injury-related cardiovascular dysfunction is essentially a diagnosis of exclusion, although the following features strongly suggest a neurogenic cause:

- no history of cardiac problems,
- temporal relationship between brain injury and cardiovascular abnormalities,
- ECG changes in isolation,
- modest elevations in cTnI,
- new onset LV dysfunction,
- cardiac wall motion abnormalities that do not correspond with coronary vascular territories,
- inconsistency between echocardiographic and ECG findings,
- inconsistency between cTnI and LV ejection fraction (cTI <2.8 μg litre^{-1} in association with LV ejection fraction <40%),
- spontaneous, early resolution.

Prognosis

Neurogenic cardiovascular abnormalities are associated with increased morbidity and mortality, although most patients who die

Table 1 Relative risks for cardiac abnormalities and the occurrence of death, poor neurological outcome, and delayed ischaemic neurological deficit after SAH. Modified from van der Bilt and colleagues.[1] DCI, delayed cerebral ischaemia; N/A, data not available from meta-analysis; RWMA, echocardiographic evidence of regional wall motion abnormalities; cTnI, cardiac troponin I; CK-MB, creatine phosphokinase-myocardial fraction; BNP, B-type natriuretic peptide

	Relative risk (95% confidence interval)		
	Death	Poor outcome	DCI
RWMAs	1.9 (1.2–2.9)	N/A	2.1 (1.2–3.8)
Elevated cTnI	2.0 (1.2–3.4)	2.3 (1.5–3.6)	3.2 (2.3–4.4)
Elevated CK-MB	2.7 (0.99–7.5)	2.3 (1.1–4.6)	2.9 (1.9–4.5)
Elevated BNP	11.1 (4.7–26.0)	N/A	4.5 (1.8–11.4)
ST depression	2.1 (1.5–3.1)	2.4 (1.9–3.0)	2.4 (1.2–4.9)
ST elevation	1.4 (0.8–2.4)	1.4 (0.9–2.0)	2.1 (0.7–5.7)
T wave abnormalities	1.8 (1.4–2.4)	1.5 (1.1–2.2)	0.9 (0.5–1.7)
QTc interval prolongation	1.2 (0.6–2.5)	1.2 (0.9–1.7)	1.0 (0.5–2.3)
Bradycardia	0.6 (0.4–0.99)	N/A	N/A

do so because of their brain injury.[1,2] What is unclear is whether neurogenic cardiac injury is independently associated with poor outcome or whether it is an epiphenomenon reflecting the severity of the underlying brain injury. A recent meta-analysis, including 25 studies and 2690 patients, quantified the relative risk of ECG abnormalities, release of biomarkers of cardiac injury and RWMAs on mortality, poor neurological outcome, and delayed ischaemic neurological deficit after SAH (Table 1).[1]

With the possible exception of prolongation of the QTc interval (which is a risk factor for torsades de pointes ventricular tachycardia), neurogenic cardiovascular dysfunction is not necessarily fatal in its own right. Its adverse effects on outcome are therefore likely to occur through consequent adverse effects on secondary brain injury and also because it is associated with longer intensive care unit length of stay and higher levels of therapeutic support. Because patients with a more severe neurological deficit are more likely to develop cardiac dysfunction, increased vigilance is required in those with the most severe brain injury. Cardiovascular diagnostic tests may help stratify patients into groups who are at greater or lesser risk of developing neurogenic cardiac injury but whether such stratification will assist in guiding treatment or prognostication remains to be seen. Further studies are therefore required to establish whether there is a causal relationship between neurogenic cardiac injury and neurological outcome, and to explore potential treatment options.

Declaration of interest

None declared.

References

1. van der Bilt IAC, Hasan D, Vandertop WP *et al.* Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. *Neurology* 2009; **72**: 635–42
2. Zygun D. Non-neurological organ dysfunction in neurocritical care: impact on outcome and etiological considerations. *Curr Opin Crit Care* 2005; **11**: 139–43
3. Lim HB, Smith M. Systemic complications after head injury: a clinical review. *Anaesthesia* 2007; **62**: 474–82
4. Nguyen H, Zaroff JG. Neurogenic stunned myocardium. *Curr Neurol Neurosci Rep* 2009; **9**: 486–91
5. Tung P, Kopelnik A, Banki N *et al.* Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke* 2004; **35**: 548–51
6. Wittstein IS, Thiemann DR, Lima JA *et al.* Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; **352**: 539–48
7. Frangiskakis JM, Hravnak M, Crago EA *et al.* Ventricular arrhythmia risk after subarachnoid hemorrhage. *Neurocrit Care* 2009; **10**: 287–94
8. Grunsfeld A, Fletcher JJ, Nathan BR. Cardiopulmonary complications of brain injury. *Curr Neurol Neurosci Rep* 2005; **5**: 488–93
9. Bruder N, Rabinstein A. Cardiovascular and pulmonary complications of aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2011; **15**: 257–69
10. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. *Curr Opin Anaesthesiol* 2008; **21**: 544–51
11. Deibert E, Barzilai B, Braverman AC *et al.* Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. *J Neurosurg* 2003; **98**: 741–6
12. Tung PP, Olmsted E, Kopelnik A *et al.* Plasma B-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. *Stroke* 2005; **36**: 1567–9
13. Banki N, Kopelnik A, Tung P *et al.* Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic dysfunction in patients with subarachnoid hemorrhage. *J Neurosurg* 2006; **105**: 15–20
14. Kopelnik A, Fisher L, Miss JC *et al.* Prevalence and implications of diastolic dysfunction after subarachnoid hemorrhage. *Neurocrit Care* 2005; **3**: 132–8
15. Castillo Rivera AM, Ruiz-Bailen M, Rucabado AL. Takotsubo cardiomyopathy—a clinical review. *Med Sci Monit* 2011; **17**: RA135–47