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CRITICAL CARE (STEPHAN A. MAYER, SECTION EDITOR)

Neurogenic Stunned Myocardium in Severe Neurological Injury

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Abstract

Purpose of Review Neurogenic stunned myocardium (NSM) is a poorly recognized cardiac manifestation of neurological illness. This review addresses the contemporary understanding of NSM pathophysiology, epidemiology, diagnosis, and clinical management.

Recent Findings While the precise pathophysiology and diagnosis remain unclear, NSM is phenotypically atypical stress cardiomyopathy that can be partially attributed to excess catecholaminergic toxicity. NSM is a diagnosis of exclusion where electrocardiography, echocardiography, and cardiac biomarkers are frequently abnormal. Clinical expertise is crucial to evaluate and differentiate NSM from acute coronary syndrome and in the evaluation of potential cardiac transplantation donors after unsalvageable severe neurological injury.

Summary Neurogenic stunned myocardium is a relatively common and clinically impactful condition. More research is needed, particularly to refine clinical prognostication of NSM and rule out intrinsic cardiac injury in order to optimize donor candidacy in the event of brain death.

Keywords Neurogenic stunned myocardium · Stress cardiomyopathy · Takotsubo cardiomyopathy · Subarachnoid hemorrhage · Severe traumatic brain injury

Introduction

Neurogenic stunned myocardium (NSM) refers to a cardiotropic response to an inciting neurological event that results in acute reversible myocardial dysfunction. NSM has been associated with a wide variety of acute neurological pathologies: aneurysmal subarachnoid hemorrhage (SAH) [1], intracerebral hemorrhage [2], traumatic brain injury (TBI) [3], acute ischemic stroke (AIS) [4], seizure [5, 6], acute hydrocephalus due to neurocysticercosis [7], encephalitis [8], spinal cord infarction [9], pediatric brain tumor [10], electroconvulsive therapy [11], and acute motor axonal neuropathy [12]. This review will address the contemporary understanding of pathophysiologic mechanisms, epidemiology, diagnostic criteria, treatment, and prognosis of NSM.

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Pathophysiology

The capacity for intracranial pathology to dynamically alter cardiac function has been known at least since the first description of the Cushing reflex over one century ago [13, 14]. Similarly, the capacity of the myocardium to develop acute reversible dysfunction has been known for decades, although this concept of myocardial stunning originally described persistently dysfunctional ischemic myocardium after coronary revascularization [15].

NSM is a form of stress cardiomyopathy (i.e., Takotsubo cardiomyopathy, broken heart syndrome, or apical ballooning cardiomyopathy) [16••]. In stress cardiomyopathy, a precipitating physical or emotional stressor triggers acute reversible myocardial dysfunction likely via exaggerated sympathetic stimulation [17]. While typical Takotsubo cardiomyopathy

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manifests as apical ballooning, NSM may have a basal ventricular cardiomyopathy predominance [18]. In this case, NSM can be thought of as an atypical variant of stress cardiomyopathy.

The mechanism for NSM is commonly attributed to catecholamine excess, but systemic inflammation and neuroendocrine derangements may also contribute to its development. Autopsy findings of focal myocardial necrosis after a severe neurological injury have been attributed to catecholamine excess [19, 20]. Additionally, systemic catecholamine levels are frequently elevated after severe neurological injury and positively correlate with NSM [21]. The commonly proposed mechanisms for the neurocardiac effects of these excess catecholamines are predominantly derived from literature regarding pathophysiology of stress cardiomyopathy and include the following: (1) epicardial coronary vasospasm, (2) acute coronary microcirculatory dysfunction causing subendocardial ischemia, and (3) catecholamine-mediated direct myocardial injury [22–24].

The link between epicardial coronary vasospasm and NSM has been demonstrated via intracoronary acetylcholine testing where left ventricle (LV) apical ballooning was reproduced after induction of iatrogenic coronary vasospasm [25]. Clinically, however, a direct correlation between coronary vasospasm and NSM has been limited to isolated case reports [26]. Of note, the left anterior descending (LAD) coronary artery typically supplies blood flow to the anterior and apical walls of the LV and is implicated in ischemia-mediated regional dysfunction in that territory. However, the isolated basal LV dysfunction often seen with NSM commonly covers a myocardial territory that extends beyond the typical distribution of a single epicardial coronary vessel. Thus, while limited evidence supports epicardial coronary vasospasm with resultant myocardial ischemia and reperfusion as a mechanism for stress cardiomyopathy, proximal epicardial vasospasm does not completely explain the development of NSM.

Acute coronary microcirculatory dysfunction coupled with subendocardial ischemia [27, 28], may also play a key role in stress cardiomyopathy. Physiologically, the small coronary arteries receive autonomic innervation and may constrict due to alpha-adrenic activity [29]. Moreover, high levels of circulating catecholamines may increase cardiac contractility and heart rate, causing increased myocardial oxygen demand. This increase in oxygen demand coupled with decreased coronary perfusion, due to vasospasm or endothelial dysfunction, may exacerbate any resultant myocardial ischemia. Perivascular myocardial vacuolization seen in autopsies of patients with epilepsy and sudden death [30] may reflect both small vessel coronary vasospasm and coronary microcirculatory dysfunction.

Catecholamine-mediated direct myocardial injury has been shown to originate in the hypothalamus with experiments showing electrical stimulation to the ventromedial hypothalamic zone leading to increased serum catecholamine levels and altered levels of tissue catecholamine concentrations [31]. Local norepinephrine release from myocardial sympathetic nerves may explain why NSM occurs in patients with normal serum catecholamine levels [32]. Importantly, a baboon model of brain death demonstrated that total cardiac sympathectomy can prevent neurally mediated cardiac injury [33]. Disease processes with excess circulating catecholamines, such as pheochromocytoma, have demonstrated the mechanism of catecholamine-mediated toxicity leading to focal myocarditis [34]. A proposed mechanism for this myocardial cellular injury is via cyclic AMP–mediated intracellular calcium overload [35]. Cardiac magnetic resonance imaging supports this mechanism [36]. Genetic polymorphisms predisposing to catecholamine-mediated myocardial toxicity are not well understood but presumably contribute to the heterogenous incidence of NSM after neurological injury [37, 38].

However, systemic inflammation and neurohormonal changes may also be key contributors as catecholamine excess does not appear to fully explain all cases of NSM. The potential for systemic inflammation to contribute to acute reversible myocardial dysfunction has been well described in sepsis and termed septic cardiomyopathy [39]. Similarly, a systemic inflammatory response syndrome has been correlated with the development of NSM after TBI [40]. A pre-clinical model of NSM demonstrated a post brain death pathophysiologic progression from a transient hyperdynamic response followed by significant decreases in systemic vascular resistance, coronary blood flow, and finally LV function [41]. Crucially, this same pre-clinical model demonstrated reversal of LV dysfunction with normalization of coronary perfusion pressure [41]. While this model does not fully account for excess catecholaminergic effects, it does support the sepsis model of peripheral vasodilation and diminished coronary blood flow contributing to reversible myocardial dysfunction. Neurohormonal changes also occur after severe neurological injury. Failure of both anterior and posterior pituitary gland leads to decreases in the anti-diuretic hormone, cortisol levels, and thyroid hormone activity [42]. Moreover, alterations in autonomic and limbic system function may contribute to the development of stress cardiomyopathy [43]. Given the neuroanatomic correlation with neurocardiac injury, it is plausible that acute intracranial events may mediate NSM through autonomic and/or limbic system derangement as well.

Clinical Considerations

Epidemiology

The incidence of NSM after acute neurological injury ranges from 20 to 40% depending on the associated neurological trigger. Severe brain injury is more frequently associated with

NSM with up to 40% of patients with brain death having myocardial dysfunction [44]. NSM is perhaps most commonly associated with SAH (incidence approximately 30% [45]) and severe TBI (incidence approximately 22% [46]), although it can also be present in AIS (incidence estimated at 1.2% from a single-center study [47]). However, the severity of the TBI may influence the development of post-traumatic NSM with episodes occurring predominantly after moderate-to-severe TBI [48•]. Risk factors for the development of NSM after SAH are the severity of neurologic injury, age, tobacco use, posterior aneurysm location, and possibly female gender [49–51]. Risk factors for the development of cardiac complications after AIS are severity of neurological injury and structural injury to the insular cortex [52].

Diagnosis

There are no formal diagnostic criteria for NSM. The diagnosis of NSM is a phenotypic description and a diagnosis of exclusion that must incorporate a wide differential diagnosis that excludes primary cardiac and metabolic pathologies (Table 1). Cardiac conduction abnormalities on electrocardiogram (ECG), myocardial function on cardiac imaging, and elevated cardiac biomarkers consistent with myocardial injury are the primary diagnostic components for NSM. However, these findings are not unique to NSM, and coronary ischemia and acute myocardial infarction remain the most important differential diagnoses [53]. In fact, autopsy data suggests that myocardial infarction is the cause of death in 12% of patients after hemorrhagic stroke [57]. Similarly, ECG abnormalities, regional myocardial dysfunction, elevated cardiac biomarkers, and AIS can also be a manifestation of systemic embolization either from endocarditis or an intra-cardiac thrombus [58].

Stress cardiomyopathy may manifest with similar cardiac functional and biochemical abnormalities after an acute neurological disorder as delineated by an international expert consensus that defined diagnostic criteria for stress cardiomyopathy [59•]. The International Takotsubo Diagnostic Criteria (InterTak) diagnostic score was originally developed to differentiate stress cardiomyopathy from ACS [60] but may provide some assistance in differentiating NSM from ACS. Although the InterTak Diagnostic Score was not specifically designed to assess NSM, the presence of an underlying neurologic disorder is one of the assessed variables.

Regardless, the core finding in NSM and other forms of stress cardiomyopathy is a new reversible, regional wall motion abnormality extending beyond the territory perfused by a single epicardial coronary artery or without evident ACS. While the diagnostic nuances are not universal nor clearly established across society guidelines, we would agree with the InterTak Diagnostic Criteria that effectively includes NSM as an atypical variant of Takotsubo syndrome [59•].

Electrocardiogram

ECG abnormalities are commonly seen in patients with NSM, particularly diffuse, deep T-wave inversions [18]. These broad, deep, and symmetric T-wave inversions are not specific for NSM, as similar findings have been described in other acute neurological conditions for over 70 years [61]. An additional and crucial mechanism for such prominent T-wave abnormalities is impending occlusion of the left anterior descending coronary artery and is referred to as "Wellens' syndrome" [62]. Other ECG abnormalities—particularly Q waves, QS waves, and non-specific ST-segment or T-wave changes—in patients with acute intracranial pathology are similarly not specific for NSM as these ECG abnormalities also correlate with the development of neurogenic pulmonary edema in patients with subarachnoid hemorrhage [63].

Moreover, the presence of any ECG abnormality may be seen in up to 90% of all patients with ischemic stroke and intracerebral hemorrhage, which may partly reflect the frequency of baseline cardiovascular disease in this population [64]. Notably, ST-segment elevation is often seen in typical Takotsubo cardiomyopathy but may not be a prevalent finding in NSM [18]. Thus, deviations from a stereotypically normal ECG are commonly seen in patients with NSM; however, no ECG pattern is specific for the diagnosis of NSM.

Echocardiogram

Echocardiographic abnormalities are the primary criteria for diagnosing NSM, with new myocardial dysfunction being the core clinical finding in NSM. The anatomic pattern of myocardial dysfunction in NSM may be global hypokinesis or more focal hypokinesis with regional wall motion abnormalities. Global hypokinesis may be more specific for TBI, whereas regional hypokinesis is observed after TBI, SAH, and ICH [44]. In contrast to the apical ballooning (due to apical and mid-ventricular hypokinesis with hyperdynamic basal segments) of typical stress cardiomyopathy, NSM may more commonly manifest as basal and mid-ventricular hypokinesis [18, 65]. This inverted stress cardiomyopathy with focal basal and mid-ventricular hypokinesis is sometimes referred to as a "reverse takotsubo" pattern or atypical basal Takotsubo cardiomyopathy [59•, 66].

However, acute SAH has also been associated with ST-segment elevation and apical-predominant regional wall motion abnormalities consistent with a typical Takotsubo cardiomyopathy pattern [67, 68]. Finally, abnormalities in global longitudinal strain using speckle tracking doppler echocardiographic imaging of the LV may be more sensitive for myocardial dysfunction after SAH [69]. The presence of RV strain abnormalities may also help differentiate stress cardiomyopathy from regional myocardial dysfunction due to LAD ischemia [70]. Moreover, abnormalities in LV global longitudinal strain and RV strain

Table 1 Differential diagnoses for patients with a severe neurological injury who present with cardiac dysfunction

Differential diagnosis	Pathophysiology	Electrocardiogram	Myocardial function	Cardiac biomarker	Coronary angiography
Acute coronary syndrome (Type 1 myocardial infarction) [53]	Unstable coronary plaque rupture	New ischemic ECG changes including the following: • ST-segment elevation in contiguous coronary leads • Diffuse ST-segment depression • New pathologic Q waves Non-specific findings: • Diffuse, deep T-wave inversions • Non-specific ST-segment or T-wave changes	New regional wall motion abnormality in a pattern consistent with a vascular territory	Troponin elevated to high levels in all patients with STEMI and NSTEMI	Identification of a coronary thrombus or occlusion Consideration of coronary revascularization as clinically indicated
Type II myocardial infarction [53]	Mismatch between coronary blood flow supply and myocardial oxygen demand, not due to unstable coronary plaque	New ischemic ECG changes including the following: • Diffuse ST-segment depression • New pathologic Q waves Non-specific findings: • Diffuse, deep T-wave inversions • Non-specific ST-segment or T-wave changes	New regional wall motion abnormality in a pattern consistent with a vascular territory	Troponin elevation in all patients	Fixed coronary atherosclerosis may be present; however, no coronary thrombus is identified
Neurogenic stunned myocardium/-stress cardiomyopathy	Acute neurological pathology • Traumatic brain injury • Subarachnoid hemorrhage • Intracerebral hemorrhage Severe emotional or physical stress response Severe autonomic dysfunction • Guillain-Barre syndrome • Pheochromocytoma	ECG abnormalities commonly seen • QTc prolongation diffuse, deep T-wave inversions, or peaked T-waves • ST-segment elevation across multiple precordial leads can occur • Q waves, QS waves, and non-specific ST-segment or T-wave changes	New reversible, regional wall motion abnormality beyond the territory perfused by a single epicardial coronary artery • Typical Takotsubo: apical-predominant Atypical Takotsubo: Basal and/or mid-ventricular hypokinesis • Global hypokinesis Reversibility of myocardial function in days to weeks	Mild elevation in below the extent expected based on the degree of LV dysfunction (often < 2.8 ng/ml [55]) Elevated troponin after SAH is sensitive (100%) and specific (91%) for myocardial dysfunction [56]	Angiography to exclude acute plaque rupture and AMI, particularly LAD disease causing antero-apical hypokinesis

Table 1 (continued)

Differential diagnosis	Pathophysiology	Electrocardiogram	Myocardial function	Cardiac biomarker	Coronary angiography
		Prompt resolution of ECG changes expected, often within 1 day [54]			
Septic cardiomyopathy [39]	Sepsis	Non-specific findings: • Diffuse, T-wave inversions • Non-specific ST-segment or T-wave changes	New reversible left ventricular global dysfunction	Mild elevation in troponin is common	Angiography only if clinically indicated to exclude acute plaque rupture and AMI

ECG, electrocardiogram; *STEMI*, ST-elevation myocardial infarction; *NSTEMI*, non-ST elevation myocardial infarction; *AMI*, acute myocardial infarction; *AIS*, acute ischemic stroke; *TBI*, traumatic brain injury; *LAD*, left anterior descending artery

derived from speckle tracking strain echocardiography are associated with in-hospital mortality after SAH [71•]. More research is needed to further elucidate the role of strain parameters and advanced cardiac imaging in the assessment of NSM [72].

Biomarkers

Limited data exists on the role of biomarkers in the diagnosis or management of NSM. An elevated cardiac troponin assay may be seen in up to one-quarter of patients with AIS, but clearly differentiating between NSM and an acute myocardial infarction may require further advanced cardiac imaging or coronary angiography [73]. Regardless, an elevated cardiac troponin after acute stroke is associated with an increased frequency of cardiac complications and mortality [74]. Similarly, cardiac troponin elevation is present in 30% of patients after severe blunt TBI and is positively associated with both the severity of head injury and mortality [75, 76]. The specific utility of cardiac troponin beyond a biomarker of risk remains unclear though. However, an elevated cardiac troponin may accurately indicate myocardial dysfunction after SAH, with a sensitivity of 100% and a specificity of 91% [56]. Another prospective cohort of patients with SAH identified ECG changes and troponin elevation as independent risk factors for early or late left ventricular wall motion abnormalities [77]. In this population, the presence of a relatively small troponin elevation, less than 2.8 ng/ml, despite at least moderate LV dysfunction, LV ejection fraction less than 40%, may differentiate NSM from a Type 1 myocardial infarction [55]. Brain natriuretic peptide (BNP), another cardiac biomarker, has also been shown to correlate with cardiac dysfunction after SAH [78]. BNP elevation does not correlate with mortality after SAH however, and the specific utility of BNP as a risk marker also remains unclear [79].

Coronary Imaging

In the case of diagnostic uncertainty or concern for acute coronary syndrome, coronary imaging should be considered. However, many patients after an acute intracranial event are clinically unstable or have a contraindication to the administration of systemic anticoagulation in the cardiac catheterization laboratory. When available, invasive coronary imaging remains the gold standard for the identification and management of unstable coronary plaque [80]. Increasingly though, coronary computed tomographic angiography (CTA) has become an option for the non-invasive evaluation of coronary anatomy in more stable patient settings [81]. The role of CTA in the evaluation of cardiac dysfunction after neurologic injury is promising but remains to be evaluated and should not replace invasive coronary angiography for the management of acute coronary syndromes.

Prevention and Treatment

NSM is often managed conservatively as reversibility of LV dysfunction is common. There is no clear role for pharmacological therapy. A meta-analysis of three retrospective studies found that pre-admission beta-blocker use did not reduce the incidence of myocardial dysfunction after SAH [82]. However, another retrospective review found that beta-blocker therapy was associated with improved survival in patients with severe TBI and an elevated cardiac troponin [75]. Similarly, a small randomized trial of anti-catecholaminergic therapy with propranolol and phentolamine after SAH found reduced LV necrotic lesions on autopsy when compared with placebo [83]. At this time, no definitive evidence exists for routine use of anti-catecholaminergic therapy to prevent NSM.

Table 2 Synonyms for neurogenic stunned myocardium

Stress cardiomyopathy
Apical ballooning syndrome
Takotsubo cardiomyopathy
Takotsubo syndrome
Broken heart syndrome
Acute reversible myocardial injury
Atypical basal Takotsubo cardiomyopathy
Reverse Takotsubo pattern

If the initial LV dysfunction persists, medical management should follow cardiovascular guidelines for heart failure with reduced ejection fraction with the initiation of appropriate neurohormonal antagonists, including beta-blockers and inhibitors of the renin-angiotensin-aldosterone system [84]. Additionally, high-dose insulin can be an appropriate therapy for acute myocardial dysfunction, such as after beta-blocker or calcium-channel blocker poisoning [85]. Scant case reports of NSM after SAH and AIS correlate the administration of high-dose insulin therapy with recovery of myocardial function [86, 87]. However, more research is needed before high-dose insulin therapy can be routinely recommended for NSM.

Arrhythmias are also a possible manifestation of neurocardiac injury, and telemetry monitoring should be considered during the acute period [88, 89]. Finally, limited case reports exist on NSM causing hemodynamic instability and requiring inotropic and temporary mechanical circulatory support [90, 91]. Limited evidence suggests that inotropic therapy with dobutamine or milrinone after SAH is well-tolerated and successfully augments cardiac output [92, 93]. Such severe NSM causing cardiogenic shock should prompt expert cardiovascular consultation with the initiation of medical and cardiac device therapy when appropriate for acute decompensated heart failure [94].

Clinical Outcome

Generally, the clinical outcome of patients with NSM is primarily associated with the severity of neurological injury, and myocardial recovery is expected. A consecutive patient cohort with aneurysmal clipping after SAH noted the prompt resolution of ECG changes, often within 1 day post-operatively [54]. A prospective study with serial echocardiography after SAH also noted recovery of LV function in 66% of patients within 1 week [45]. However, even reversible cardiac dysfunction does not necessarily reflect a benign clinical course. A dedicated registry and systematic review of stress cardiomyopathy suggests an increased rate of long-term overall mortality, particularly in older patients with physical stressors and atypical Takotsubo patterns [95, 96]. Cardiac dysfunction after SAH is also an independent predictor for poor clinical outcome and an increased risk of mortality [50, 97].

The appropriate diagnosis and management of NSM is also crucial in the evaluation of potential cardiac transplantation donors after an unsalvageable severe neurological injury that progress to brain death [98]. Given the limited availability of donor organs, reversible donor cardiac dysfunction due to NSM should not be a strict limitation for transplantation eligibility as prompt myocardial function recovery has been seen [99]. Crucially, clinical outcomes after cardiac transplantation of a donor heart with transient LV systolic dysfunction, including NSM, have been found to be comparable to outcomes with a normal LV ejection fraction donor heart [100•].

Conclusion

NSM is a common finding present in a broad range of severe neurological injuries. While the precise pathophysiology remains unclear, NSM is likely synonymous with several types of reversible cardiomyopathies (Table 2) but is phenotypically predominated by atypical basal stress cardiomyopathy that can be partially attributed to excess catecholaminergic toxicity. ECG abnormalities, myocardial dysfunction, and cardiac biomarker elevation are frequently present. Treatment is supportive; specific management recommendations are lacking and generally follow heart failure guideline recommendations. More research is needed, particularly to refine clinical prognostication of NSM and optimize donor candidacy after brain death.

Compliance with Ethical Standards

Conflict of Interest Benjamin B. Kenigsberg, Christopher F. Barnett, Jeffrey C. Mai, and Jason J. Chang each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Clinical Vignette

A 40-year-old previously healthy man, with a prior echocardiogram showing normal left ventricle (LV) size and left ventricular ejection fraction (LVEF) 65%, mild aortic regurgitation, and aortic root dilatation, is admitted with a Hunt Hess 2/Fisher Grade 4 subarachnoid hemorrhage. An external ventricular drain is emergently placed for hydrocephalus. Conventional angiography reveals a ruptured right posterior communicating artery aneurysm that is coiled. The patient is started on nimodipine and seizure prophylaxis. Transcranial dopplers and clinical exam are performed to monitor for cerebral vasospasm.

On hospital day 5, a chest radiograph (CXR) ordered for dyspnea shows prominent cardiomegaly and mild pulmonary edema. A subsequent echocardiogram identifies a severely dilated LV with severe global hypokinesis, a LVEF 20–25%, and moderate aortic regurgitation and aortic root dilatation.

Medical therapy with a beta-blocker, angiotensin receptor blocker, and diuretics are administered with a resolution of clinical heart failure symptoms. During his month-long hospitalization, no cerebral vasospasm or new adverse events occur. He is discharged home with ongoing outpatient physical therapy. Repeat echocardiogram after six weeks shows normalization of LV function with a LVEF of 55–60% along with moderate aortic regurgitation.