Cardiac Dysfunction After Neurologic Injury

What Do We Know and Where Are We Going?

Vijay Krishnamoorthy, MD, MPH; G. Burkhard Mackensen, MD, PhD; Edward F. Gibbons, MD; and Monica S. Vavilala, MD

Recent literature has implicated severe neurologic injuries, such as aneurysmal subarachnoid hemorrhage, as a cause of cardiac dysfunction, impaired hemodynamic function, and poor outcomes. Mechanistic links between the brain and the heart have been explored in detail over the past several decades, and catecholamine excess, neuroendocrine dysfunction, and unchecked inflammation all likely contribute to the pathophysiologic process. Although cardiac dysfunction has also been described in other disease paradigms, including septic shock and thermal injury, there is likely a common underlying pathophysiology. In this review, we will examine the pathophysiology of cardiac dysfunction after neurologic injury, discuss the evidence surrounding cardiac dysfunction after different neurologic injuries, and suggest future research goals to gain knowledge and improve outcomes in this patient population.

CHEST 2016; 149(5):1325-1331

KEY WORDS: cardiomyopathy; critical care; neurology

The idea of an “invisible” link between the brain and heart has been recognized for centuries.¹ For example, although sudden death after severe fright and emotional stress has been reported in ancient texts for centuries, a greater interest in brain-heart interactions has been seen in the medical literature over the past several decades.^{2,3} In addition, a growing body of literature has implicated other neurologic injuries, especially aneurysmal subarachnoid hemorrhage (SAH), as a cause of cardiac dysfunction. Although SAH has received the most in-depth study, the body of literature regarding brain-heart interactions in other neurological conditions is more limited.

Some mechanistic links between the brain and the heart have been explored in detail and are considered to be plausible explanations for the observed clinical symptoms. Although cardiac dysfunction has been described in other disease states, including septic shock^{4,5} and thermal injuries,⁶ there may be a common link regarding catecholamine excess and unchecked inflammation. In this review, we will examine the known pathophysiology of cardiac dysfunction after neurologic injury and suggest a common unifying pathophysiological process, explore the current state of knowledge in various neurologic injury paradigms, and discuss

ABBREVIATIONS: cAMP = cyclic adenosine monophosphate; CBN = contraction-band necrosis; CI/RI = cardiac ischemia/reperfusion injury; NSM = neurogenic stunned myocardium; RWMA = regional wall motion abnormalities; SAH = aneurysmal subarachnoid hemorrhage; TBI = traumatic brain injury; TSM = Takotsubo cardiomyopathy

AFFILIATIONS: From the Departments of Anesthesiology and Pain Medicine (Drs Krishnamoorthy, Mackensen, and Vavilala) and Medicine (Dr Gibbons) and the Harborview Injury Prevention and Research Center (Drs Krishnamoorthy, Gibbons, and Vavilala), University of Washington, Seattle, WA.

FUNDING/SUPPORT: This work was funded by National Institutes of Health National Research Service Award [grant T32 GM086270].

CORRESPONDENCE TO: Vijay Krishnamoorthy, MD, MPH, Anesthesiology and Pain Medicine, University of Washington, 1959 NE Pacific St, BB-1469, Seattle, WA 98195; e-mail: vkkrish@u.washington.edu
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DOI: <http://dx.doi.org/10.1016/j.chest.2015.12.014>

future directions for research into these complex disorders.

Neurogenic Stunned Myocardium vs Stress Cardiomyopathy

Cardiac dysfunction after neurologic injury is currently classified either as neurogenic stunned myocardium (NSM) or stress-induced cardiomyopathy (ie, Takotsubo cardiomyopathy [TSM], also known as “broken heart syndrome”).⁷ Of particular note are the general location (basal in NSM vs apical in TSM) of the myocardial dysfunction, and the predilection toward the female sex, which is more common in TSM^{8,9} as compared with NSM.¹⁰ Furthermore, there is debate as to whether NSM and TSM are distinct entities or simply represent different manifestations of a similar underlying pathophysiologic pathway, ultimately resulting in cardiac dysfunction.¹¹ A review suggested that the clinical and pathophysiologic similarities between the two syndromes suggests a revision of the diagnostic criteria⁷; in fact, the updated Mayo Clinic criteria for diagnosis of TSM includes intracranial hemorrhage.¹² In light of the debate in nomenclature as well as the heterogeneous nature of NSM, we will refer to this state more generally as “cardiac dysfunction” throughout the remainder of this article.

Pathophysiology of Cardiac Dysfunction After Neurologic Illness

A growing body of data is beginning to uncover the complex interactions between the impaired brain and the heart and is summarized in Figure 1, with clinical examples in Videos 1 and 2. Several basic science studies have highlighted the role of the sympathetic nervous system and catecholamine release on cardiac biomarker elevation and histologic evidence of myocardial damage in a variety of animal models.^{13–17} Preclinical experiments have been validated by clinical findings of cardiac dysfunction in prospective studies, case series, and case reports. Although SAH¹⁸ and emotional distress³ remain major disease paradigms in which we draw mechanistic information, cardiac dysfunction has been reported after virtually every major injury to the neurologic system.⁷

Excess catecholamines are central to the pathophysiology of brain-heart interactions. The initial injury to the brain activates pathways of catecholamine release through a variety of mechanisms. Independent of the specific injury type, three key factors are involved at the level of the brain: the location of the lesion, rises in intracranial pressure, and the activation of the lower brain neuroendocrine pathways from the hypothalamus.

A set of experiments by Oppenheimer and Cechetto¹⁹ helped to map the particular areas of the brain with autonomic effects, determining a central role of the

Figure 1 – Mechanisms and clinical implications of cardiac dysfunction after neurologic illness. BNP = brain natriuretic peptide; cAMP = cyclic adenosine monophosphate.

insular cortex, both in control of cardiovascular function and modulation of the autonomic nervous system. The insular and subcortical regions of the brain have been implicated in the evolution of an increased sympathoadrenal tone in both SAH and stroke²⁰; and damage to these regions results in a complex cascade of catecholamine release, autonomic dysfunction, and neuroinflammation.²¹ Elevated intracranial pressure also activates the autonomic nervous system, releasing catecholamines from sympathetic nerve endings in the myocardium.²¹ Interestingly, the absolute systemic values of catecholamine levels rarely have any correlation to the severity of the cardiac dysfunction,²² likely emphasizing the importance of local catecholamine concentration in the myocardium.

The mechanism of myocyte injury involves not only local catecholamine excess, but also elevated intracellular calcium and reperfusion injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic adenosine monophosphate (cAMP)-mediated calcium overload²³; at the most basic physiologic level, the release of catecholamines into the myocardial interstitium leads to prolonged opening of beta-1-adrenergic receptor-controlled calcium channels and rapid depletion of adenosine triphosphate. The myocardial injury is exacerbated by the effects of reperfusion,²⁴ likely stimulated by further calcium influx. Cardiac necrosis is greater near the nerve terminals in the endocardium and is progressively less severe with progression to the epicardium.²⁵

The end result of the catecholamine storm at the level of the myocardium is mitochondrial dysfunction and cell death with the resulting classic histologic finding of contraction-band necrosis (CBN), which 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 to areas of sympathetic innervation rather than specific vascular territories. Pathologically, CBN is characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear infiltrate; this is in contrast to the polymorphonuclear inflammation seen with infarction.³ CBN has also been described in other states of catecholamine excess such as pheochromocytoma.^{26,27} CBN is found in about 26% of patients after noncerebral death; this proportion increases to 89% of patients after SAH and 52% of patients after stroke demonstrating histologic evidence of CBN,²⁸ with the severity of cardiac dysfunction being

closely related to the severity of the underlying brain injury.²⁹

There has also been growing interest into the secondary role of the inflammatory cascade in brain-heart interactions. Neurologic injury can trigger a neuroinflammatory response, including release of cytokines and adhesion molecules from the brain into the systemic circulation; this mechanism has been implicated in the pathogenesis of arrhythmias after SAH.³⁰ The activation of the sympathetic nervous system (coupled with parasympathetic dysfunction) can also lead to unchecked myocardial inflammation, resulting in myocardial cell death and cardiac dysfunction.²¹

Clinical Pathophysiologic Studies

Clinical studies have provided further insight into the mechanism, cardiac dysfunction patterns, and outcomes of cardiac dysfunction following neurologic injury. Local catecholamine release likely explains why absolute serum catecholamine levels rarely correlate with the severity of cardiac dysfunction after brain injury.²² Banki et al³¹ studied scintigraphic images of myocardial uptake of technetium sestamibi and meta-[¹²³I]iodobenzylguanidine to assess both perfusion and sympathetic innervation of the myocardium, respectively, in patients with SAH. Although perfusion remained normal in all of the studied patients, almost 30% of these patients had evidence of “functional myocardial sympathetic denervation”; furthermore, they were more likely to have regional wall motion abnormalities (RWMA) on echocardiography, hypotension, and increased doses of vasopressors. The authors postulated that excessive catecholamine release from myocardial sympathetic nerves may cause damage to both the cardiomyocytes and the innervating nerve terminals themselves.³¹ A further consequence of local catecholamine release is potential microvascular vasospasm of blood vessels supplying the myocardium,³ as explained by reduced coronary flow reserve and regional defects on cardiac meta-[¹²³I]iodobenzylguanidine scintigraphy, suggesting the presence of sympathetically mediated microcirculatory dysfunction.³² Further evidence of a local sympathetically mediated contribution is supported by the observation that the base of the heart commonly demonstrates the most severe abnormalities, an area known to have a higher norepinephrine content and a greater density of sympathetic nerves compared with the apex^{33,34} and referred to in case reports as “inverted TSM.”³⁵ Last, polymorphisms in adrenoreceptors have been associated

with increased cardiac dysfunction after SAH,³⁶ further highlighting the importance of the catecholamine-myocardium interface in the overall neurocardiac interaction.

A well-reported example that documents brain-heart interaction in humans pertains to acute emotional stress, where it has been implicated in sudden death. Over the past several decades, a variety of reports^{8,37,38} have emerged in the literature aiming to better understand this phenomenon.³⁹ Wittstein et al³ described the course of echocardiographic findings in 19 patients with cardiac dysfunction after an acute emotional stressor, which rapidly resolved in all of the patients. In this study, elevated plasma catecholamine levels were documented; furthermore, histologic findings on myocardial biopsy specimens were consistent with CBN, suggesting excessive sympathetic stimulation as a possible underlying mechanism for the observed clinical symptoms. A similar pathophysiologic mechanism may underlie most brain-heart interactions in humans.²⁴ Despite differing underlying mechanisms in stress cardiomyopathies compared with acute coronary syndromes, recent observational data suggest similar rates of in-hospital complications in both disease entities, including the presence of shock and in-hospital mortality.⁴⁰

The primary manifestation of clinically relevant cardiac dysfunction after neurologic injury described in the literature pertains to left ventricular dysfunction. Other cardiac manifestations of the brain-heart interaction include arrhythmias,²⁸ ischemic-like ECG changes,¹⁰ repolarization abnormalities,⁴¹ hypotension,⁴² and release of cardiac-specific biomarkers.^{43,44} Although extensive research over the past several decades has shed more light on the pathophysiology of brain-heart interactions, many questions still remain including the exact role of the inflammatory cascade, identifying susceptible patients, identifying high-risk neurologic lesions, and targeting appropriate therapies for these conditions.

Neurologic Disorders and Cardiac Dysfunction

Although cardiac dysfunction has been well-documented in populations with SAH, it has also been documented after other causes of intracranial bleeding, stroke,⁴⁵ CNS infection,⁴⁶ traumatic brain injury (TBI),^{42,47} brain death,^{48,49} and epilepsy.⁵⁰ Other critical care syndromes (ie, sepsis) are also known to be associated to cardiac dysfunction,^{51,52} with suspected similarities in mechanisms to NSM.⁵³

Subarachnoid Hemorrhage

NSM has been observed in approximately 20% to 30% of patients with SAH,¹⁸ with evidence of decrements in ejection fraction or RWMA.⁵⁴ Clinical predictors of NSM in this population include neurologic injury severity,⁵⁵ elevated troponin levels, elevated brain natriuretic peptide, and female sex.^{10,53,54} Patients with SAH have an increase in plasma norepinephrine (3 fold compared with the general population) within 48 h after the initial insult; this persists during the first week of injury and normalizes by 6 months.⁵⁶ In addition, elevated troponins have been documented in more than 30% of patients with SAH and are associated with greater degrees of cardiac dysfunction (ejection fraction < 50% or RWMA score > 1).⁵⁷ Observational studies examining cardiac dysfunction after SAH have not only documented cardiac dysfunction by ECG, but several also have reported increased mortality and poorer neurologic outcomes independent of SAH alone.^{10,58,59} Although adverse mechanisms remain unclear, they are postulated to involve both global and regional manifestations of cardiac dysfunction, including poorer perfusion to injured regions of the brain.⁵⁷

Ischemic Stroke

Ischemic stroke is another neurologic syndrome that has shown associations with cardiac dysfunction, although has been less well-studied than other “classic” neurologic disorders that are associated with cardiac dysfunction. Ischemic stroke is associated with a 75% to 92% risk of development of new ECG abnormalities,⁴⁵ with reports documenting myocardial stunning, similar to that seen in SAH.⁶⁰ Lesion location in stroke may be particularly important because right-sided strokes, especially involving the insula and parietal lobe, are associated with the development of cardiac dysfunction.⁶¹ These findings may reflect the underlying autonomic balance in the brain, including a potential right-sided sympathetic dominance and left-sided parasympathetic dominance.⁶²

Epilepsy

Epilepsy is another neurologic syndrome with a potential association with cardiac dysfunction. In the phenomenon of sudden death after epilepsy, several investigators have implicated cardiac dysfunction and the induction of lethal arrhythmias as a potential cause^{63,64}; available data suggest both T-wave changes and periods of bradycardia and even asystole during refractory seizures.⁶⁵ Furthermore, in patients with prolonged seizures, norepinephrine levels increase during the phase of generalized seizures and remain high

for several hours.⁶⁶ This significant catecholamine elevation may reflect a common underlying pathophysiologic pathway that is shared with other brain-heart syndromes.

Infection

Neurologic infections such as encephalitis have also been implicated as a cause of cardiac dysfunction, especially in severe cases with associated cerebral edema and elevated intracranial pressure.^{46,67,68} Although many cases of cardiac compromise after a myriad of central nervous system infections have been reported, enteroviral brainstem encephalitis has been exquisitely linked to cardiopulmonary dysfunction, causing patients, who were primarily children, to present with both pulmonary edema and shock.^{69,70} Although a primary viral myocarditis cannot be fully ruled out, cardiac autopsy studies and measurement of neuroinflammatory markers suggest a primary neurogenic origin to cardiac dysfunction during brainstem encephalitis.⁶⁸

Brain Death

The intersection between catastrophic neurologic deterioration and cardiac dysfunction is perhaps best exemplified in patients with a brain death diagnosis. Recent clinical data suggest that about 30% of adult patients with a diagnosis of brain death have either an ejection fraction < 50% or evidence of RWMA on ECG, with approximately one-half of these patients showing improvement in cardiac function over several days.⁴⁸ Using a mouse model, Atkinson et al⁷¹ investigated the effect of donor brain death on posttransplantation cardiac ischemia/reperfusion injury (CI/RI) and showed that donor brain death enhances complement activation and exacerbates CI/RI in transplanted cardiac grafts. In addition, they demonstrated a clinical correlation between complement activation and inflammation in hearts from brain-dead vs living donors. These data suggest novel treatment opportunities using complement inhibition to ameliorate brain death-exacerbated CI/RI.⁷¹ Patterns of initial cardiac dysfunction followed by improvement suggest neurogenic stunning as the underlying etiology, and may have a particular implication with donor resuscitation to maximize organ availability before transplantation, as the current cardiac donor pool is limited.

Traumatic Brain Injury

TBI, an entity in which hypotension has been exquisitely linked to poor outcomes,⁷² has recently emerged as also

being associated with cardiac dysfunction.⁴² ECG data in patients with TBI suggest that QT prolongation and repolarization abnormalities are associated with cardiac dysfunction,⁷³ which is a similar finding in other neurologic injury paradigms. Furthermore, observational data in patients with TBI suggest that beta-blocker exposure during hospitalization is associated with favorable outcomes, including reduced in-hospital mortality⁷⁴; this may be secondary to attenuation of the effects of catecholamine excess that is central to the pathophysiology of most brain-heart interactions. The management of cardiac dysfunction in the TBI population may be especially important because it may have a role in preventing secondary brain injury from hypotensive episodes.

Heart-Brain Interactions

In addition to the many brain-heart interactions discussed previously, it is also important to understand that several “heart-brain” interactions occur as well, in which the primary mode of injury to the brain is driven by the heart, rather than injury to the heart driven by the brain. The vast number of pathophysiologic insults to the brain initiated at the level of the heart (atrial fibrillation with cerebral emboli, low cardiac output states, etc.) are beyond the scope of this review. Because of different underlying pathophysiologic processes underlying brain-heart and heart-brain interactions, treatment paradigms for these syndromes differ widely. Although the previously described brain-heart syndromes all have clinically distinctive features, it is postulated that cardiac dysfunction after the entire gamut of neurologic syndromes may share similar pathophysiologic mechanisms. Thus, cardiac dysfunction after primary neurologic illness may improve with similar treatment modalities.

Clinical Management

The hemodynamic profile secondary to catecholamine storming initially includes hypertension, followed by hypotension secondary to unopposed vasodilation and cardiac dysfunction secondary to coronary vasoconstriction, myocardial ischemia, and cell death, even in the absence of coronary atherosclerosis.²¹ Despite the heterogeneity of disease entities that cause this condition, the basic principles of management include maintenance of normal hemodynamics and excellent supportive care. Beyond these basic principles, though, the nuances of hemodynamic management are often dictated by the underlying disease. As examples, management of TSM secondary to SAH includes

maintaining cerebral perfusion in the setting of cerebral vasospasm⁵⁴; in contrast, in TBI, cerebral perfusion may largely be affected by impaired cerebral autoregulation rather than cerebral vasospasm.⁷⁵ Additionally, cardiomyopathy secondary to acute anxiety would only require maintenance of a minimally acceptable BP. Last, although sympathetic blockade through alpha- or beta-blockade would seem relevant, clinical data on the utility of beta-blockade are conflicting,^{40,76} and robust data are lacking on the optimal drug, dose, and timing to best optimize patient outcomes.

Conclusion

Cardiac dysfunction has been described after a variety of neurologic injuries and emotional stressors. The pathophysiology likely involves a complex interplay of the neuroendocrine system, neuroinflammation, and systemic and local catecholamine release. Further research is necessary to evaluate cardiac dysfunction more extensively in neurologic injuries outside of SAH, to better understand the impact of cardiac dysfunction on patient outcomes, and to test therapeutic strategies that may either prevent or attenuate the development neurogenic cardiac dysfunction.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The Videos can be found in the Multimedia section of the online article.

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