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NEUROCRITICAL CARE SOCIETY

REVIEW

Cardiac Dysfunction in Neurocritical Care: An Autonomic Perspective

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Abstract

A number of neurologic disorders can cause cardiac dysfunction by involving the conductive system and contractile apparatus of the heart. This is especially prominent in the neurocritical care setting where the spectrum of cardiac dysfunction due to acute neurologic injury ranges from trivial and isolated electrocardiographic changes to malignant arrhythmias and sudden death (Table 1). The mechanism of these cardiac complications is complex and not fully understood. An understanding of the neuroanatomical structures and pathways is of immense importance to comprehend the underlying pathophysiology that culminates as cardiac damage and dysregulation. Once the process is initiated, it can complicate and adversely affect the outcome of primary neurologic conditions commonly seen in the neurocritical care setting. Not only are these cardiac disorders under-recognized, there is a paucity of data to formulate evidence-based guidelines regarding early detection, acute management, and preventive strategies. However, certain details of clinical features and their course combined with location of primary neurologic lesion on neuroimaging and data obtained from laboratory investigations can be of great value to develop a strategy to appropriately manage these patients and to prevent adverse outcome from these cardiac complications. In this review, we highlight the mechanisms of cardiac dysfunction due to catastrophic neurologic conditions or due to stress of critical illness. We also address various clinical syndromes of cardiac dysfunction that occur as a result of the neurologic illness and in turn may complicate the course of the primary neurologic condition.

Keywords: Autonomic nervous system, Sudden death, Neurocardiology, Cardiac dysfunction in critical care

Background and Historical Landmarks

The concept of psychological stress causing sudden cardiac death can be found in anthropological literature. The first detailed scientific account of these 'psychosomatic deaths' was by Cannon et al. in his famous 1942 publication "Voodoo Death." The mechanism proposed by Cannon et al. to explain these 'cardiac' deaths was neurogenic, specifically, a severe and persistent sympathoadrenal response [1]. Half a century before Cannon's work, the association of sympathetic stimulation and sudden death already had begun to unfold, but in a different context.

In the late nineteenth century, there were reports of an increasing number of intraoperative deaths in England and Wales. Initially, these deaths were attributed to cardio-inhibitory effect of chloroform overdose. However, the sequence of events leading to these deaths described in case reports in 1890s revealed that deaths occurred during the recovery phase from chloroform anesthesia rather than deep sedation. Interestingly, the deaths ensued when a strong painful stimulus was applied to the patient during lighter phase of sedation [2]. Armed with this knowledge, Levy et al. performed a series of experiments on cats and demonstrated that sympathetic activating maneuvers, such as intravenous adrenaline administration, electrical stimulation of sympathetic cardiac nerve or emotional stress, all of which triggered ventricular fibrillation. More importantly, these effects were seen exclusively during light chloroform sedation,

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suggesting that a neural mechanism was responsible for these arrhythmias and not chloroform overdose [3, 4].

A decade later, Neuberger et al. reported a case series of five patients who died during seizures and were found to have myocardial lesions with normal coronary vessels [5]. Additionally, in animal models, myocardial lesions without involvement of coronary vessels could be produced by imparting stress to metabolically deranged rats [6, 7]. These lesions were pathologically different from liquefactive necrosis of acute myocardial infarction, and adrenalectomy did not prevent development of the lesions [7]. Raab et al. also demonstrated that reserpine, a drug that blocks catecholamine release from presynaptic adrenergic nerve terminals, prevented these stress induced lesions. However, drugs which blocked circulating catecholamine did not have the same effect [6]. Additionally, in a clinical case series of patients who died acutely from an aneurysmal subarachnoid hemorrhage, Greenhoot et al. found discrete necrotic lesions with interstitial hemorrhage in myocardium. Similar myocardial lesions were reproduced in adult cats with stimulation of reticular formation in midbrain. Interestingly, these necrotic lesions were clustered around nerve endings of the heart [8].

All these findings in animals and clinical studies point toward sympathetic overactivity, either due to stress or severe neurologic damage, which initiates a process that culminates in release of excessive catecholamine at cardiac post-synaptic adrenergic receptors.

In order to understand the mechanisms by which neurologic disorders change the autonomic balance, we briefly discuss the neuroanatomical pathways between the nervous system and heart.

Neuroanatomical Perspective

Introduction

The autonomic nervous system is a widespread network of nerves that connects central nervous system to the visceral organs. Sympathetic and parasympathetic fibers are the peripheral efferents of this neural network that innervate and modulate their targets organs, such as receptors on the heart and vascular walls and smooth muscles of visceral organ. However, the origin and subsequent governance of these peripheral efferents occur in cell bodies clustered in nuclei, distributed at various locations in central nervous system (Fig. 1). This forms a central neuronal network that controls vital functions.

Sensory Nervous System of Heart (Fig. 1)

Sensory receptors in the heart are distributed throughout myocardial, pericardial and epicardial tissue and at the junction of atria and great veins. These receptors are activated by pressure in the heart chambers, and impulses are transmitted, predominantly via vagal afferent to

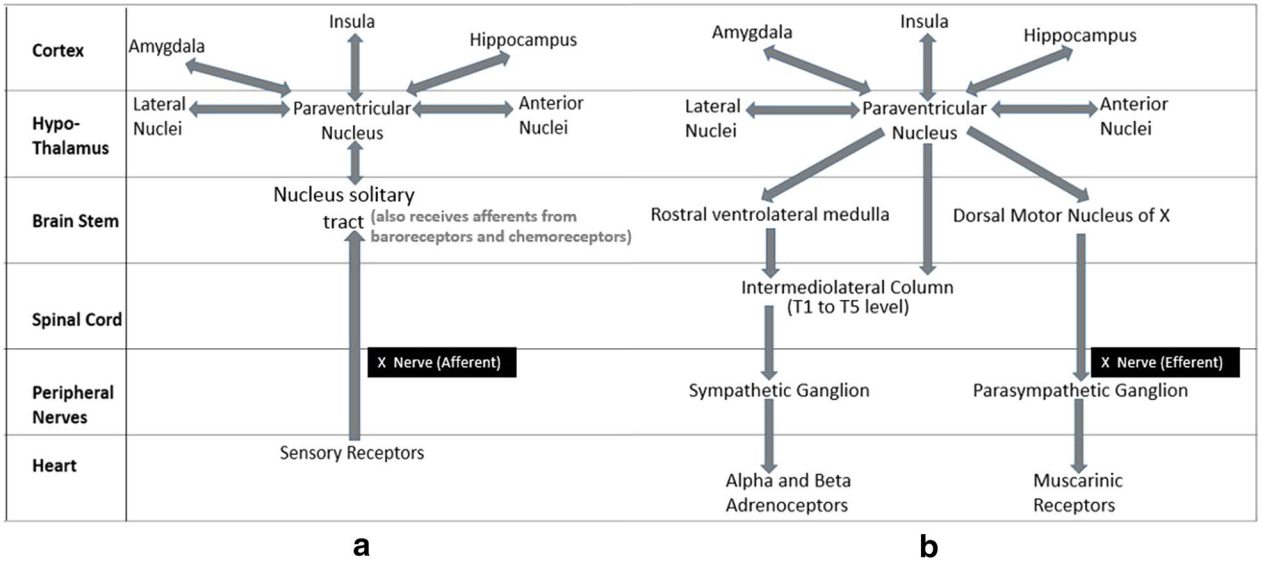


Fig. 1 Autonomic-cardiac network: **a** afferent connections from sensory receptors of heart travels via IX and X cranial nerves to nucleus solitary tract in medulla. Periventricular nucleus of hypothalamus is an integrating center as it has reciprocal connections (bidirectional arrows) with autonomic nuclei from brain stem, other hypothalamic nuclei and from cortex. **b** Efferent autonomic pathway to the heart. Again shown are reciprocal connections of periventricular hypothalamus with other central autonomic nuclei in cortex, hypothalamus, brain stem, and spinal cord. Sympathetic efferents from higher centers descend to intermediolateral columns of upper thoracic spinal cord, whereas parasympathetic signals travel via vagus nerve

nucleus of solitary tract (NTS) in the medulla. NTS also receives afferents from baroreceptors, chemoreceptors and skeletal muscle receptors [9].

Intrinsic Nervous System of Heart

Centrally derived autonomic nerves, as discussed in subsequent sections, are considered the dominant regulator of cardiac function. However, there is evidence suggesting presence of an intrinsic network of cell bodies with interconnecting fibers, collectively known as cardiac ganglionic plexus (CGP). Dominantly cholinergic, the CGP has been considered as relay station to parasympathetic efferents [10]. However, due to a number of factors, they have been increasingly recognized as a nervous system intrinsic to the heart. Firstly, they contain other neuromodulators such as nitric oxide (NO), vasoactive intestinal polypeptide, neuropeptide Y and intermedin in addition to traditionally known autonomic neurotransmitters. Secondly, specific receptors for each of these neuromodulators are present in the heart (Table 4).

Parasympathetic stimulation interacts with sympathetic stimulation to counter various aspects of arrhythmogenesis. Intrinsic CGP along with these neuromodulators plays a role in this interaction as detailed in Table 4. These actions of CGP are mediated by both modulation of acetylcholine effects and effects of these neuromodulators on their specific receptors.

Extrinsic Nerve Supply of Heart

Table 4 depicts neurotransmitters and autonomic receptors of heart and effects of their stimulation via sympathetic and parasympathetic nerve endings. Beta2 receptors, located predominantly on the basal segments and less commonly on the apical segments of the heart, are the most dominant recipients of sympathetic nerve supply. This distribution of sympathetic receptors plays a pivotal role in etiopathogenesis of neurologic and neurogenic cardiac dysfunctions as described in more detail in later sections. The sympathetic nerve supply to the heart arises from cardiac plexus, a bundle of nerves at arch of aorta. The nerves in cardiac plexus are post-ganglionic projections arising from paravertebral sympathetic cervical and upper thoracic ganglions. The paravertebral sympathetic ganglions in turn receive descending input from higher centers which exit central nervous system (CNS) via upper five thoracic spinal cord segments as preganglionic fibers (Fig. 1). Parasympathetic nerve supply to the heart has its preganglionic neurons located dominantly in nucleus ambiguus and to lesser extent in dorsal medial nucleus of vagus. Descending vagal pathways converge directly on CGP as described in the previous section.

Higher Centers and Descending Pathways (Fig. 1)

As discussed above, efferent vagal nerve fibers from the nucleus ambiguous and dorsal vagal nucleus transmit parasympathetic signals to the heart [11]. Sympathetic input to the heart comes from neurons in the intermediolateral (IML) column at T1 to T5 level of spinal cord. This IML column is modulated by descending neurons from rostral ventrolateral medulla and paraventricular nucleus (PVN) of hypothalamus [11].

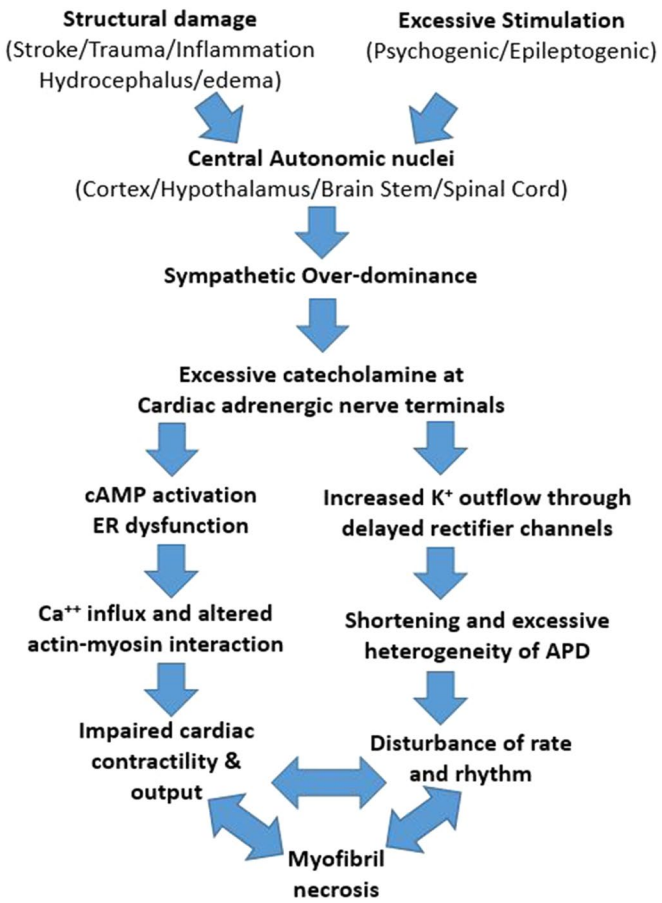
Parvocellular neurons in PVN of hypothalamus, also known as pre-autonomic neurons, are the only autonomic neurons which are recipients of autonomic afferents and send both sympathetic and parasympathetic efferents to other autonomic centers. Thus, PVN is considered to be the control center, modulating and optimizing balance between two opposite responses [12].

Other hypothalamic nuclei that play an important role in cardiovascular regulation are anterior and lateral hypothalamic nuclei. In animal studies, stimulation of anterior hypothalamus produced bradycardia, whereas an opposite response was seen with stimulation of lateral hypothalamus. This suggests that anterior hypothalamus has parasympathetic whereas lateral hypothalamus has a sympathetic influence over the heart [13].

In higher cortical centers, especially the insula, control of sympathetic and parasympathetic outflow is lateralized in a complex manner. Studies of unilateral hemispheric inactivation with ipsilateral intra-carotid amobarbital injection [14–16], intraoperative stimulation of insular cortex [17], and positron emission tomography scans during physical and mental stress all revealed that sympathetic response was lateralized to the right insula and parasympathetic activity to the left [18]. In studies of patients with stroke, results are conflicting. Involvement of insula on either side was associated with excessive sympathetic activity, but was more pronounced in patients with right insular stroke [19, 20]. Additionally, in animal studies, sympathetic chronotropic activity was found to be represented at rostral posterior insula, whereas parasympathetic chronotropy localized to caudal posterior insula [21].

Pathogenesis and Pathophysiology

Several different mechanisms have been proposed to explain neurogenic myocardial dysfunction. The most widely accepted of these is focal damage or dysfunction of CNS structures controlling autonomic outflow (Fig. 2) leading to sympathetic over-dominance which in turn affects myocardial rhythm and integrity. Myocardial autonomic innervation and its impact on myocardial pathophysiology depend on multiple factors.



Abbreviations: cAMP=cyclic adenosine monophosphate, ER=endoplasmic reticulum, APD=Action potential duration

Fig. 2 Pathophysiology of autonomic cardiac dysfunction

Physiology of Myocardial Contraction

Diastolic interval (DI) is the resting state of myocyte during which membrane potential inside the cell membrane is more negative relative to the outside. This polarized state is achieved and transiently maintained, predominantly due to the outward flow of potassium (K^+) through rectifier K^+ channels (Fig. 3a).

DI ends when electrical impulses lead to the onset of action potential (AP) by rapid opening of fast inward sodium (Na^+) channels and consequent rapid Na^+ influx into the cell. This initiates a new state, the systole, which lasts for a duration corresponding to the AP duration (APD). Electrographically, this duration is represented by QT interval, i.e., summation of durations of QRS complex, ST segment, and T waves. APD is maintained transiently as calcium ($Ca^{++)}$ flows in through L type Ca^{++} channels. At the end of APD, delayed rectifier potassium (K^+) channels slowly open leading to K^+ efflux, thus ending APD by restoration of polarized state [22].

Heterogeneity of Ventricular Sympathetic Response

A number of studies have shown that there is a heterogeneity of sympathetic supply among various walls and segments of myocardium. Base of the left ventricle is richly innervated by sympathetic nerves [23]. Ng et al. demonstrated that during sympathetic stimulation, there was shortening of APD that was significantly more pronounced at the base. Furthermore, expression of delayed rectifier potassium channels through which catecholamine produces shortening of APD was highly upregulated in basal area during sympathetic stimulation [24].

Effect of Sympathetic Stimulation (Fig. 3b)

Sympathetic stimulation via its effect on delayed rectifier potassium channels directly affects AP and reduces its duration [24]. In canine models, slow rectifier K^+ channels do not contribute to change in APD during the resting state, but cause significant APD shortening during beta adrenergic stimulation [25]. Heart rate (HR), which is the sum of DI and APD, tends to increase as both of its

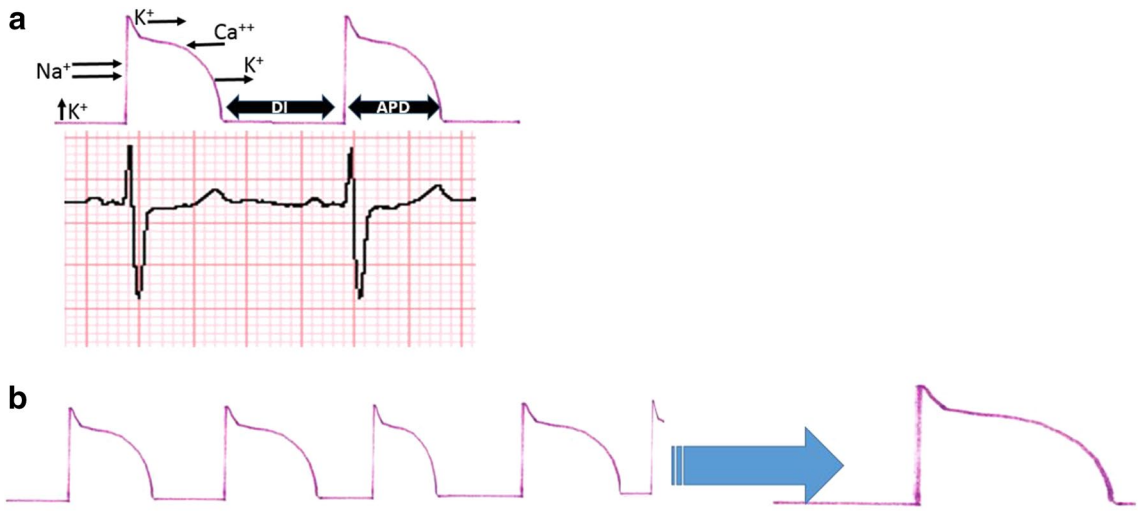


Fig. 3 **a** Top panel: diastolic interval (DI) is the resting (polarized) state of myocytes due to outward flow of K via slow rectifier channels. This period ends with the onset of action potential leading to depolarization (systole) initiated by rapid influx of Na. This state is maintained by Ca influx and ends by K efflux through slow rectifier channels. Action potential duration (APD) corresponds to QT interval shown in bottom panel. **b** Myocardial action potential during ongoing sympathetic stimulation. Shown is a relatively shorter first beat (first AP cycle with minimal shortening of DI and APD). For maintenance of constant HR, next cycle has relatively longer DI and APD, which in turn giving rise to much shorter DI and APD (AP restitution described in text). This sequence of long and short cycles (AP alternans) if continued due to ongoing sympathetic stimulation will ultimately lead to an AP duration longer than refractory period thus setting forth wave break and potentially, malignant arrhythmias

components are shortened. Shortening of DI has another very crucial consequence (Fig. 3b). Through a feedback mechanism attempting to keep HR under control, this shortened DI will lead to APD prolongation of next cycle [26, 27]. This phenomenon of dependency of APD of a given cardiac cycle on DI of its preceding cycle is known as *restitution of APD* [28].

At rest, the curve of this relationship of DI to APD of the subsequent beat is relatively flat, i.e., magnitude of change in APD is not significantly greater than the change in DI of previous cycle. With sympathetic stimulation, the slope of this curve steepens; a small change in DI causes a marked change in AP duration of subsequent cycle. If sympathetic stimulation is prolonged, this phenomenon initiates a rhythm disturbance known as AP alternans, i.e., a series of cardiac cycles with shorter and longer durations alternating with each other (Fig. 3b) [29].

During this course of sympathetic stimulation, AP duration can be prolonged to the extent that a new stimulus may arise while myocardial cells are still in refractory period of AP, leading to malignant arrhythmia by setting off a wave break or reentry [24, 29, 30]. Electrographically, this process corresponds to prolonged QT interval. Moreover, it also further affirms the clinical importance of correcting QT interval according to HR. Magnano et al. demonstrated that in 25 healthy subjects, isoproterenol infusion resulted in QT interval shortening that was much less for a given increase in HR. As a result, QT interval corrected for HR was prolonged [31].

AP alternans, described above is a precursor of malignant arrhythmias and predictor of sudden death [32]. The heterogeneity of sympathetic distribution among different walls and segments of ventricles can get exaggerated which promotes occurrence of AP alternans and consequently malignant arrhythmias [33].

Besides steepening of AP restitution curve via its effect on delayed rectifier K^+ channels, sympathetic stimulation also significantly alters Ca^{++} levels by affecting L type Ca^{++} channels. This leads to triggered activity as well as after depolarizations, both of which are known precursors of ventricular arrhythmias.

Self-Perpetuation of Sympathetic Effects

Increased sympathetic activity in the heart leads to a phenomena, known as sympathetic neural remodeling (SNR). This involves nerve sprouting and further hyperinnervation of sympathetic nerves which has shown to cause malignant arrhythmias and sudden death [34]. In rats that are subjected acute myocardial ischemia, the oxidative stress has shown to increase sympathetic activity and further stimulate SNR by promoting expression of nerve growth factor gene [35]. This mechanism can have potential therapeutic implications. Lithium, for example, by activating antioxidant gene regulators, has shown to inhibit NGF expression and thus protects

against ventricular arrhythmias. Intermedin, a member of calcitonin gene-related peptides that act via calcitonin receptors-like receptors and receptor activity-modifying protein (table), has also shown to inhibit oxidative stress and SNR in rats with heart failure due to acute MI. These effects in turn lead to reduced occurrences of ventricular arrhythmias and heart failure [36].

Degeneration and Necrosis of Myocytes

Excessive catecholamine exposure results in increased activity of cAMP in myocytes causing excessive Ca^{++} influx. Actin–myosin interaction can be prolonged enough to overwhelm their physical integrity. Severe and prolonged catecholamine stimulation is well known to produce myofibrillar degeneration and contraction band necrosis [37]. Characteristically located in sub-endocardium, these band necrotic lesions are known to produce malignant arrhythmias by involving the conducting tissue [38]. Additionally, dysfunctions of protein synthesis by endoplasmic reticulum causing apoptosis have also been implicated in myocardial damage in rats who were subjected to traumatic stress [39].

Interaction of Parasympathetic and Sympathetic responses

Muscarinic receptors, supplied by a network of cholinergic post-ganglionic fibers, are distributed throughout the ventricles [40]. In addition to directly producing negative inotropic and chronotropic effects, this network is a potent inhibitor of adrenergic response. The later effect is mediated by effect of acetylcholine on M3 subtype muscarinic receptors, located at presynaptic sympathetic nerve terminals. Experimental studies involving enhancement of parasympathetic activity via vagal nerve stimulation (VNS) found that there was flattening of APD restitution slope, increase in effective refractory period and hence increase in ventricular fibrillation threshold. Not surprisingly, VNS was found to be protective against ventricular arrhythmias [41, 42]. However, antiarrhythmic effect of vagal stimulation was seen only during simultaneous sympathetic stimulation and this protection was lost with left stellate ganglionic ablation [42]. This 'counter sympathetic' effect also decreases sympathetic induced exacerbation of heterogeneity between basal and apical segment of myocardium, thus preventing ventricular fibrillation.

In addition to all these cholinergic actions mediated via muscarinic receptors, intrinsic cardiac ganglionic plexus as discussed in previous section, along with a number of neuromodulators (Table 4), further facilitate this interaction of two opposing mechanisms in order to maintain homeostasis.

Clinical Features and Syndromes: Conductive Disturbances

Impaired Electrical Activity of Heart

Electrocardigraphic (EKG) changes are common in patients with neurologic catastrophes. In patients with acute stroke, repolarization abnormalities particularly QTc prolongation were most common. However, due to similar vascular risk factors, a preexisting coronary artery disease rather than neurogenic mechanism may be responsible for these EKG changes in a number of patients. Yet, QTc prolongation and to some extent other repolarization abnormalities, if present during acute phase of stroke, may be suggestive of a neurogenic mechanism. Goldstein et al., by comparing EKGs of patients obtained during acute phase of stroke with their previous EKGs, found new QTc prolongation to be present in 32% of these patients compared to 2% of controls [43].

Another striking EKG feature in patients with stroke is the presence of abnormal T waves, which are seen in almost 30% of patients with stroke [44]. In a study of 150 patients with stroke and age-matched controls, new T wave inversion and U waves were present in 15% of patients with acute stroke but not in any patient from the control group [43]. These T waves are sometimes also referred to as "cerebral T waves" and defined as a T wave inversion ≥ 5 mm in depth in ≥ 4 contiguous precordial leads. A retrospective analysis of 800 patients with stroke showed presence of T waves in 17 patients (2.1%). Even more, approximately 20% of patients with T wave inversion had transient wall motion abnormalities on the echocardiogram consistent with stress-induced cardiomyopathy [45]. Table 3 highlights the major EKG abnormalities in ischemic and hemorrhagic strokes.

Remarkably, QTc prolongation is not only a potential indicator of underlying neurogenic mediated cardiac dysfunction but also may be a strong predictor of devastating cardiac and neurologic complications. In an outpatient study of stroke survivors of all types, prolonged QTc in lead V6 was associated with a threefold increase in mortality with specificity approaching 94% for QTc interval ≥ 4.8 ms [46]. Also, QT prolongation along with tachycardia at baseline EKG was found to be independently associated with development of cerebrovascular spasm [47]. Another study from the Czech Republic showed that QTc prolongation after 48 h of stroke was associated with mortality. Almost 40% of patients who died during hospitalization after an acute stroke were found to have prolonged QTc after 48 h of stroke onset [48].

Cardiac Arrest and Sudden Death

Neurologic diseases are the leading cause of sudden death of non-cardiac origin, especially in the younger population [49].

Sudden and unexpected deaths due to neurologic catastrophes are best exemplified by acute aneurysmal sub-arachnoid hemorrhage (aSAH) patients who die before reaching the hospital. These sudden deaths occur in 11–17% of patients with aSAH [50–53]. In Rochester, Minnesota, over a period of three decades, 113 patients with ruptured intracranial aneurysm were studied. Of these 113 patients, 13 (12%) died suddenly before reaching the hospital. Posterior circulation aneurysm was more frequent (38%) in patients with sudden death. In comparison, posterior circulation aneurysm was present only in 14% of patients who survived the initial insult. Interestingly, intraventricular hemorrhage was present in 12 of these 13 patients with sudden death. Autopsy findings of these patients did not reveal any structural cardiac abnormalities [51].

Data regarding sudden death are not as extensive in other subtypes of acute stroke. However, sudden and unexpected deaths seem to occur in the subacute or delayed phase of stroke. A 3-month follow-up of patients who were enrolled in placebo arm of randomized trial of trilizad in acute stroke (RANTTAS) showed that unexplained cardiac arrest occurred in 2% of these 279 patients [54]. In another postmortem study of 125 patients who died within one month after supra-tentorial ischemic stroke, about 8% died suddenly and unexpectedly without any apparent cause at autopsy [55]. A published review by Soros and Hackinski gives a detailed account of sudden death in stroke patients [56].

Other than stroke, seizures are also associated with sudden death [57]. A prospective study of 4, 578 patients with epilepsy showed occurrence of Sudden Unexpected Death in Epilepsy (SUDEP) at an incidence rate of 1.2/1000 patients per year. SUDEP was responsible for 18% of all deaths in epilepsy patients [58]. A 4-year follow-up of patients in Western China found that 14.7% of all deaths in epilepsy were sudden and unexpected [59]. Furthermore, in patients with epilepsy, retrospective measurement of QT interval before and after seizures during simultaneous continuous EEG and EKG recording revealed abnormal prolongation of QT interval during 21 seizures (9 patients) out of 156 seizures recorded in 39 patients [60].

Clinical Features and Syndromes: Contactile Dysfunctions

Stress Cardiomyopathies

In 1980, Cebelin et al. used the term 'stress cardiomyopathy' to describe myofibrillar necrotic lesions of heart found at autopsy of physical assault victims. These deaths were presumably due to excessive sympathetic stimulation triggered by severe stress of assault as none of these victims had any internal organ injury to explain the deaths [61].

However, this 'neurogenic' myocardial damage is not always immediately fatal as identified a decade later in Japan by Sato and colleagues. They reported a series of cases of potentially reversible cardiomyopathy mimicking acute anterior wall myocardial infarction. These patients presented with acute onset of chest pain that was temporally related to emotional stress. EKG revealed ST segment elevation in precordial leads, but emergent coronary angiography was negative for atherosclerotic narrowing of coronary vessels. Ventriculography showed apical and diaphragmatic akinesia along with hyperkinesia of basal segment resulting in apical ballooning. This gave a peculiar shape of myocardium that was similar to 'Takotsubu'—a Japanese fishermen's octopus pot. Therefore, this cardiomyopathy, that was transient and resolved over time, was termed Takotsubu cardiomyopathy (TCM) also known as 'apical ballooning syndrome' or' broken heart syndrome' [62].

In addition to emotional stress such as death of close family or friend, financial loss or natural disasters, this cardiomyopathy is also known to be precipitated by stress related to acute critical illness such as sepsis, acute respiratory failure and catecholamine infusion [63–66].

Neurogenic Stunned Myocardium

Neurogenic stunned myocardium (NSM) is described as a syndrome of acute left ventricular dysfunction triggered by an acute neurologic condition. Despite similarities with TCM (Table 1), NSM is a distinct subtype of stress cardiomyopathy. This is due to a different triggering mechanism of NSM, in which there is a direct involvement of neural cardiovascular regulatory areas precipitated by the acute neurologic condition rather than their secondary involvement as a result of stress which is seen in TCM. The clinical, biochemical and electrographic manifestations of NSM are described in detail in Table 2.

Echocardiographic studies in patients with aSAH have shown that myocardium can be affected either: (a) globally with severe reduction of left ventricular ejection fraction (LVEF) or (b) with regional wall motion abnormalities (RWMA) with normal LVEF [67–69]. Global LV dysfunction with LVEF of < 50% can be found in 15% of patients after aSAH, whereas RWMAs are seen in 13–27% of patients after rupture of intracranial aneurysm [68, 70]. The incidence of RWMA can be even higher in patients with more severe neurologic injury due aSAH [69, 71]. More than one-third of patients with high Hunt and Hess score have RWMA on echocardiography [71]. The pattern of RWMA does not correlate with coronary distribution. Basal and mid-ventricular segments of LV are most commonly affected and apex tends to be spared,

Table 1 Overview of neurogenic cardiac dysfunction

Autonomic mediated abnormality	Proposed pathophysiologic mechanism	Clinical spectrum and disorders	Common inciting conditions
Cardiac conduction disturbance	Sympathetic over-dominance affecting myocardial ion channels leading to alteration in action potential and exaggeration of intrinsic heterogeneity Myocardial band necrosis, dominantly in sub-endocardium but may involve conducting pathways	Changes in HR Loss of HR variability EKG repolarization abnormalities Elevation of cardiac enzymes Ventricular arrhythmias Sudden death	aSAH, also seen in acute ischemic and hemorrhagic stroke, seizures, and TBI
Myocardial inotropic dysfunction	Increased catecholamine exposure to myocardium due to stress or neurologic damage producing enhanced cAMP production and ER dysfunction, Ca^{++} influx and prolongation of actin–myosin interaction. Apoptosis, inflammation and band necrosis are known to occur	Stress induced cardiomyopathy	Psychological stress, critical illness, natural disasters, medical and neurologic disorders, catecholamine infusion, spinal cord disorders
		Neurogenic stunned myocardium	All neurologic catastrophes but most often seen in high-grade aSAH

aSAH aneurysmal subarachnoid hemorrhage, *cAMP* cyclic adenosine monophosphate, *EKG* electrocardiographic, *ER* endoplasmic reticulam, *HR* heart rate, *TBI* traumatic brain injury

Table 2 Clinical features of Takotsubo cardiomyopathy and neurogenic stunned myocardium

Clinical features	Takotsubo CMP	Neurogenic stunned myocardium
Presentation	Chest pain, short of breath (pulmonary edema)	Chest pain may be masked by coma or altered mentation. Acute pulmonary edema is more common presentation
Age/gender	Overwhelming majority of females of higher age group	Majority are females of relatively younger age group. Also affects significant number of males
Inciting event	Stress (psychosocial, critical illness), no inciting event in one-third of patients	Acute neurologic catastrophe especially high-grade aSAH
EKG changes	S–T segment elevation in precordial leads are most common	S–T elevation in precordial leads is less common. QT prolongation and T wave inversions may be more frequent than TCM
Wall motion abnormalities	Apical wall motion abnormality with hypokinesia of basal segments is more common. Mid-ventricular wall motion abnormality can also be seen	Either of two patterns are more common (1) hypokinesia of basal and mid-ventricular segments with apical sparing, (2) global hypokinesia of LV
Clinical course	Significant improvement in LV function can occur in 1–2 weeks	Depends on severity of primary neurologic injury. Known to adversely affect outcome from aSAH
Complications	Hypoxemia/hypotension/SVT Ventricular arrhythmias are less common	Hypotension and ventricular arrhythmias are more frequent

aSAH aneurysmal subarachnoid hemorrhage, *CMP* cardiomyopathy, *LV* left ventricle, *SVT* supraventricular tachycardia, *TCM* Takotsubu cardiomyopathy (Refs. [60–67, 92])

a pattern which correlates with the distribution of sympathetic nerve endings [23, 67, 70].

In addition to severity of neurologic injury and female sex, ST segment elevation in anterior precordial leads, high cardiac troponin, history of cocaine and amphetamine use and posterior circulation aneurysms are known risk factors of development of NSM in patients with aSAH [71–74].

Despite paucity of data, LV dysfunction is known to occur in almost all acute neurologic conditions. In patients with acute ischemic stroke, it typically affects older age women. LV dysfunction has been reported in association with cardio-embolic stroke affecting either hemisphere, large vessel embolic stroke in posterior circulation or cryptogenic stroke involving basal ganglia (Table 3). Interestingly, 38% of patients with LV dysfunction had involvement of insula [75].

NSM can complicate the course and outcome of primary neurologic injury. Heart failure, pulmonary edema and cardiac arrhythmias are the most common complications. Development of NSM in patients with aSAH was associated with significantly higher risk of cerebral vasospasms and delayed cerebral ischemia (DCI) [74]. These complications due to NSM adversely affect long-term functional outcome and mortality [74, 76]. Additionally, low LVEF due to NSM poses a great challenge

Table 3 Clinical and electrographic cardiac events: a comparison between ischemic and hemorrhagic strokes

Cardiac event	Spontaneous ICH (%)	Ischemic stroke (%)
Incidences of cardiac events		
Deaths during hospitalization	24 (1)	4.9–8
Acute heart failure	3.8	4.4
Ventricular arrhythmias	0.3	1.1
Elevated troponin	8.5–20	6–17
Post-stroke AMI	0–0.3	0.5–2.3
Common EKG changes		
QTc prolongation	34.3	9.8
ST segment depression	11.6	22
ST segment elevation	10.2	9.8
U wave abnormality	9.6	9.8
Pathologic Q wave	13.9	17.1
Abnormal T wave	39.9	43.9

AMI acute myocardial infarction, *EKG* electrocardiographic, *ICH* intracranial hemorrhage

in treatment of DCI with hemodynamic augmentation as there is a significant increase in systemic sympathetic tone which increases LV afterload [77]. Consequently, on the one hand there is further compromise of cerebral blood flow and worsening of cerebral vasospasms, whereas on the other hand, use of vasopressors and volume infusion becomes more challenging and potentially counterproductive. Therefore, not only there is increased risk of development of cerebral vasospasm and delayed cerebral ischemia, sympathetic mediated cardiovascular dysfunction can significantly contribute to a vicious cycle that ultimately culminates in increased mortality and poor functional outcome [74].

Risk Stratification and Diagnostic Workup

Demographics and Historical Data

In various studies, older age, severity of lesion, preexisting coronary artery disease, arterial hypertension and bradycardia have been shown to be risk factors for ventricular arrhythmias [78, 79]. Patients who were already taking angiotensin converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) were less likely to develop ventricular arrhythmias than those who were not on this medications before aneurysmal rupture [78]. Furthermore, female gender, which comprises overwhelming majority of TCM cases, is more prone to develop QTc prolongation after aSAH. In a multivariate analysis, female gender and hypokalemia were identified as independent risk factors for QTc prolongation after SAH [80].

Severity of Primary Neurological Injury

Severity of primary neurological injury can also provide valuable insight regarding risk stratification. Patients who presented with a National Institutes of Health Stroke Scale (NIHSS) of > 10 had a higher rate of troponin elevation and ischemic changes in EKG compared to patients with NIHSS < 10 [81]. Similarly, patients with higher Hunt and Hess score after aSAH have a much higher incidence of left ventricular RWAs [71].

Location of Neurological Damage in Imaging

Location of neurologic damage on neuroimaging can also provide guidance for risk stratification. Posterior circulation aneurysmal rupture was much more commonly associated with sudden death as compare to anterior circulation aneurysms. Intraventricular hemorrhage was found in 12 of 13 patients with aSAH who died before reaching the hospital [51]. Another study of 118 intracranial hemorrhage patients in Japan revealed that insular involvement was an independent predictive factor of ST depression, whereas insular involvement and the presence of intraventricular hemorrhage were independent predictive factors of QTc prolongation [82].

EKG Changes

Typical EKG changes described above are an important marker of cardiac dysfunction. Serial EKG studies or continuous telemetry recording along with an echocardiogram are extremely useful in the identification of patients at risk and the diagnosis of NSM.

Biochemical Markers

Biochemical markers of myocardial damage, such as troponin T or I, are commonly elevated in patients with acute stroke even in patients without preexisting cardiac history or renal dysfunction and are associated with increased mortality at 1-month follow-up [83, 84]. However, association of this increased mortality with sudden cardiac death has not been fully evaluated. In patients with aSAH, elevation of troponin I is highly sensitive and specific marker of neurogenic myocardial damage [85]. In comparison to severity of myocardial dysfunction with low ejection fraction (EF), troponin elevation is modest. This relatively modest elevation of troponin with severely low EF on 2D Echo in aSAH is suggestive of a neurogenic process rather than acute coronary syndrome [86].

Therapeutic Options and Future Directions

Although cardiac dysfunction from neurogenic catastrophes is associated with morbidity and mortality, there are no clear guidelines for the acute management or for identification of high-risk patients. Management of these

Table 4 Overview of autonomic receptors and actions of cardiac neurotransmitters and neuromodulators

Neurotransmitter/modulator	Receptors	Actions	Consequences
Norepinephrine and epinephrine	NE: Act dominantly on bet 1 adeno-receptors, but also act on beta2, alpha1 and alpha 2 (presynaptic inhibition). EPI: released from adrenal medulla and reach via circulation	SA node activation, increased AV node and his purkinje conduction, increased inotropy increased heterogeneity during repolarization, increased slope of APD restitution, reduced VFT	Increased HR, increased cardiac output and perfusion to vital organs. Increased propensity to ventricular arrhythmias and myocardial necrosis
Acetylcholine	Muscarinic receptors (M1 to M5 subtypes) in sympathetic and parasympathetic ganglia Post-synaptic receptors (dominantly M2) in conductive tissue and myocytes of atria and ventricles Presynaptic sympathetic nerve terminal (M3 subtype)	Inhibition of SA and AV node, reduced inotropy, reduced heterogeneity and increased VFT	Reduced HR and inotropy. Reduced propensity to ventricular arrhythmias
Nitric oxide	Released in ventricles with vagal nerve stimulation. Possible existence of intrinsic nitrergic neurons in ventricles	Accentuation of vagal mediated flattening of APD restitution slope and increase in VFT	Protection from ventricular arrhythmias
Vasoactive intestinal polypeptide	Released in response vagal stimulation, cholinergic drugs, and coronary occlusion. VIP-immunoreactive fibers are located around coronary sinus and around SA and AV nodes	Coronary and peripheral vasodilation, LV afterload reduction, enhance myocardial isometric force	Improves coronary flow during reperfusion and free radical scavenger, afterload reduction
Neuropeptide Y	Released during prolonged sympathetic stimulation and act via Y2 receptors located at vagal presynaptic terminals	Reduce Ach release from parasympathetic nerve terminals and reduce vagal bradycardic response	Increased propensity to sympathetic-mediated arrhythmias.
Intermedin	Released from myocytes during ischemia and act via calcitonin receptors	Reduce sympathetic activity, increases VFT and oxidative stress	Protection from sympathetic mediated ventricular arrhythmias and heart failure in patient with acute MI

Ach Acetylcholine, *APD* action potential duration, *AV* atrioventricular node, *EPI* epinephrine, *HR* heart rate, *IMD* Intermedin, *LV* left ventricle, *MI* myocardial infarction, *NE* Norepinephrine, *NO* Nitric oxide, *NPY* Neuropeptide Y, *SA* sino-atrial node, *VFT* ventricular fibrillation threshold, *VIP* Vasoactive intestinal polypeptide

complications is generally based on the same principle as for a non-neurologic cause. However, based on the unique pathophysiology of these conditions, some specific therapeutic options can be suggested:

(1) Centrally acting sympathetic blockers are a reasonable choice for patients with high blood pressure requiring antihypertensive treatment with underlying risk factors for neurogenic cardiac dysfunction. *Clonidine*, a centrally acting alpha-2 antagonist, has been shown to suppress cardiac arrhythmias in patients with congestive heart failure (CHF) [87]. However, there is paucity of data on its effects on acute neurogenic cardiac dysfunction. Antihypertensive agents that block both central apha-2 receptors and imidazoline receptors, such as rilmenidine, have been shown to inhibit adrenaline-induced ventricular arrhythmias in halothane anesthetized dogs. However, the presence of vagal tone was critical for this action [88]. Safety of these medications as antihypertensives agents is well documented but further clinical research is needed in the neurocritical care setting. ACE-Is and ARBs are good choices for long-term blood pressure control [78]. However, choice of short- and long-term antihypertensive agents in patients who are at risk of neurogenic cardiac dysfunction is an avenue where further research is needed.

(2) Protective effect of VNS, as discussed above, has been studied in clinical trials of patients with CHF of primarily cardiac origin. It is worthwhile to mention that altered cardiac autonomic activity, specifically reduction in vagal tone in patients with CHF after myocardial infarction plays a vital role in progressive worsening of symptoms and increased risk of sudden death [89]. Two small studies have shown safety and feasibility of implantable VNS, with improvement in clinical parameters of CHF of primary cardiac origin [90, 91]. However, INOVATE-HF, a large randomized study of effect of implantable VNS in patients with CHF failed to show any mortality benefits or reduction in episodes of CHF exacerbation [92]. Feasibility and efficacy of VNS in patients with neurogenic cardiac dysfunctions is largely unexplored although a number of animal studies have shown its beneficial effect in restoring autonomic balance [87, 93]. Antiarrhythmic mechanism of parasympathetic nervous system and protective effect of VNS has been discussed comprehensively in a review [29].

(3) A number of pharmacologic agents frequently used in neurocritical care settings such as anticonvulsants, neuroleptics, or certain antimicrobial agents can prolong QTc interval and should be avoided whenever feasible, especially in patients at high risk of cardiac complications. Correction of hypokalemia and hypomagnesemia is prudent, for the same reason.

(4) In the management of DCI after aSAH, inotropic agents are preferable over vasopressors for hemodynamic augmentation, especially for patients with NSM [94–97]. Dobutamine has been shown to increase cerebral blood flow (CBF) by 50% in patients with severe vasospasm. The improvement in CBF with dobutamine was not only comparable to phenylephrine infusion, but was achieved without afterload augmenting effects of the latter. Also, dobutamine produced 20% reduction in systemic vascular resistance (SVR) [94]. In another study, neurologic deficit due to DCI was reversed in more than two-thirds of patients treated with dobutamine [95].
Milrinone, a phosphodiesterase III inhibitor which increases intracellular concentration of cyclic adenosine mono-phosphate in myocardium and vascular smooth muscles, was found to be more effective than dobutamine in patients with NSM who had higher SVR, whereas dobutamine was more effective in patients with lower SVR and blood pressure [96].
However, as with most of hemodynamic augmenting agents, effects of dobutamine and milrinone on myocardium are adrenergic. Limited data are available for efficacy of alternative methods of augmenting cardiac output (CO) such as intra-aortic balloon pump [97]. Clinical cases have been reported success of use of intravenous insulin infusion in augmenting CO in a patient with NSM secondary aSAH and acute ischemic stroke [98, 99].

(5) A number of novel treatments are being studied based on the interplay of sympathetic and parasympathetic nervous systems. NO has been investigated in animal subjects during CPR after ventricular fibrillation induced cardiac arrest and showed improved success of CPR, neurologic outcome and mortality rate [100]. A phase II, double blind trial comparing efficacy of inhaled NO with placebo is currently enrolling patients with out of hospital cardiac arrest. The primary end points of the study are effects on mortality, cardiac and neurologic morbidity.
Beside NO, intermedin, a calcitonin gene-related peptide, is another novel agent. Released from myocytes in response to ischemia, it acts on calcitonin receptors and calcitonin-like receptors (Table 4). Intermedin administration has been shown to improve cardiac function, reduce sympathetic mediated neural remodeling, and increase ventricular fibrillation threshold in rats with ischemia induced CHF [36].

Despite the agents and strategies available, there is paucity of evidence-based data addressing cardiac dysfunctions in neurologic catastrophes. Randomized clinical studies are needed for development of parameters for risk stratification, approaches for acute intervention, and strategies for long-term prevention of cardiac complications.

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Author Contribution
MI and KS were responsible for study conception, literature search, writing and editing the manuscript. BS and WM were involved in editing the manuscript.

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