Neurogenic stunned myocardium — do we consider this diagnosis in patients with acute central nervous system injury and acute heart failure?

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Abstract

Neurogenic stunned myocardium (NSM) is defined as myocardial injury and dysfunction of a sudden onset, occurring after various types of acute brain injury as a result of an imbalance in the autonomic nervous system. The typical spectrum of clinically observed abnormalities includes acute left ventricular failure, not uncommonly progressing to cardiogenic shock with hypotension that requires inotropic agents, pulmonary oedema and various arrhythmias. Commonly-seen electrocardiographic changes include: prolonged QT interval, ST segment changes, T-wave inversion, a new Q-wave or U-wave. Echocardiography shows both an impaired systolic and diastolic function of the left ventricle. Biochemical markers of NSM comprise metabolic acidosis and increased cardiac enzymes and markers: creatine kinase (CK), and CK-MB, troponin I and B-type natriuretic peptide. The main cause of NSM is myocardial injury induced by local catecholamine release from nerve endings within the myocardium. Recently, a theory has been proposed to classify NSM as one of the stress-related cardiomyopathies, together with Takotsubo cardiomyopathy, acute left ventricular failure in the critically ill, cardiomyopathy associated with pheochromocytoma and exogenous catecholamine administration. The occurrence of NSM increases the risk of life-threatening complications, death, and worsens neurologic outcome. As far as we know, treatment should generally focus on the underlying neurologic process in order to maximize neurologic recovery. Improvement in neurologic pathology leads to rapid improvement in cardiac function and its full recovery, as NSM is a fully reversible condition if the patient survives. Awareness of the existence of NSM and a deeper knowledge of its etiopathology may reduce diagnostic errors, optimise its treatment.

Key words: neurogenic stunned myocardium, cardiomyopathy, stress, acute neurologic conditions

Acute central nervous system (CNS) injury can result in cardiovascular disorders. They are the inevitable element of non-traumatic subarachnoid haemorrhage and other conditions [1]. Common abnormalities accompanying this pathology include hypertension, arterial hypotension (observed less frequently), arrhythmias, ECG changes occurring in 75–92% of patients, as well as the increased activity of cardiac enzymes and biochemical markers of myocardial injury [2]. In rare cases, circulatory disorders can predominate during the clinical course of the disease. They generally include life-threatening arrhythmias, myocardial ischaemia and, occasionally, sudden cardiac arrest.

One of the rare and poorly known pathologies is neurogenic stunned myocardium (NSM), which can develop in any acute CNS pathology. Awareness of its existence is essential as, although NSM is associated with an increased risk of severe, life-threatening complications, death and persistent neurologic disorders, it is also a fully reversible pathology provided the underlying disease has been brought under control [3].

Neurogenic stunned myocardium is defined as myocardial injury and dysfunction occurring after various types of acute brain injury due to central autonomic disorders. It has recently been suggested to classify NSM as one of the
stress-induced cardiomyopathies, together with Takotsubo cardiomyopathy induced by emotional or physical stress, cardiomyopathy of acute critical conditions (e.g. accompanying sepsis), and cardiomyopathy associated with pheochromocytoma or exogenous catecholamine administration [2].

**EPIDEMIOLOGY AND CLINICAL PICTURE**

As NSM has commonly been described in patients with subarachnoid haemorrhage [2–5], the majority of NSM data comes from studies concerning this group of patients. NSM has also been observed in individuals with ischaemic stroke [4], craniocerebral trauma [5, 6], encephalitis [7], myelitis [8], Guillain-Barre syndrome [9, 10], following neurosurgical procedures [11], as well as in those with acute hydrocephalus [12, 13], status epilepticus [14] and other acute CNS injuries. Although any acute pathology of CNS is likely to induce NSM syndrome, one’s individual predisposition seems crucial. The reasons for its development in particular patients and for the absence of cardiac dysfunction symptoms in individuals with extremely similar CNS pathologies are unknown. Polymorphism of genes encoding adrenergic receptors, which may make them more or less sensitive to stimulation, has been implicated [10]. NSM can develop at any age, less commonly in children, yet it is not known whether this reflects the actual lower incidence in this age group. As the pathology in question has been diagnosed only recently, many cases are likely to remain undiagnosed. Moreover, this is also due to the fact that NSM has not been considered previously in the differential diagnosis of acute heart failure in patients with acute CNS diseases.

The symptoms of acute left ventricular failure usually occur within the days following the development of CNS pathology [3]. The most characteristic feature of NSM is its complete reversibility and the restoration of normal myocardial function if the underlying acute neurological condition improves [2, 3, 16]. In the majority of cases, the return of normal left ventricular function is seen within 5–14 days, sometimes several weeks [2, 15]. In some cases, however, NSM leads to death [3, 17].

The typical spectrum of clinical manifestations includes acute left ventricular failure often progressing to cardiogenic shock, hypotension requiring inotropical support, as well as pulmonary oedema. The particularly common accompanying abnormalities involve arrhythmias or conduction disorders occurring in almost 100% of patients with subarachnoid haemorrhage and in 20–40% of individuals with cerebral stroke [3]. Bradycardia or sinus tachycardia, ventricular and supraventricular tachycardia, atrial fibrillation and flutter, ventricular extrasystoles, torsade de pointes, ventricular fibrillation and flutter have been observed in patients with NSM [3]. Arrhythmias most commonly develop within 48 hours following the onset of an acute neurologic condition [18]. NSM syndrome also includes electrocardiographic abnormalities, predominantly repolarisation disorders, such as a prolonged corrected QT (QTc) interval, ST segment changes, T wave inversion, a new Q wave and U wave. QTc prolongation is observed most frequently, i.e. in about 45–71% of patients with subarachnoid haemorrhage, 64% of those with intracranial haemorrhage and 38% of individuals with cerebral stroke [3, 19], and is associated with an increased risk of severe ventricular arrhythmias. The ECG changes develop early and are correlated with the severity of the neurologic injury and precede the clinical symptoms of arrhythmias. Interestingly, even the most marked ECG abnormalities often regress, sometimes spectacularly, in cases progressing to brain stem death [20]. In the absence of heart-brain neural connections (a transplanted heart, severe autonomic diabetic neuropathy or amyloidosis-associated neuropathy, stellate ganglion blockade or stellectomy, e.g. in the treatment of long QT syndrome), neurogenic heart injury is prevented [22].

Moreover, an echocardiography (ECHO) shows moderate to severe impairment of left ventricular wall contractility. The most common ECHO abnormalities include hypokinesis of the basal and intraventricular segments with sparing of the apical part or global hypokinesis of the left ventricle [2, 3, 21]. In some cases, apical or intraventricular hypokinesis not involving the basal segments is found, which is typical for Takotsubo cardiomyopathy [2]. Characteristically, the pattern of left ventricular contractility abnormalities does not correlate with the distribution of one coronary vessel. Moreover, they are transient and normal left ventricular function in survivors is restored within few days/weeks [2].

Laboratory tests have shown transient metabolic acidosis, increased activity of cardiac enzymes and elevated concentrations of myocardial injury markers [2, 3]. Furthermore, increased activity of creatinine kinase (CK) and its cardiac isoenzyme (CK-MB), elevated concentrations of cardiac troponins and B-type natriuretic peptide (BNP) are observed. An increase in cardiac troponin I (cTnI) correlates with the extent of left ventricular dysfunction and the severity of the neurologic condition [2]. According to a retrospective study carried out by Bulsar et al. [23], in NSM, an increase in cTnI concentrations is usually moderate, despite marked contractility abnormalities. Indeed, the authors find this observation helpful for the differentiation of NSM from myocardial infarction. On the other hand, increased BNP concentrations correlate with the extent of myocardial damage, left ventricular dysfunction, reduced ejection fraction, pulmonary oedema and the risk of early death [23].

If NSM is not taken into consideration in the differential diagnosis of acute heart failure in patients with acute neurologic pathology, it leads to misdiagnosis, most commonly of acute coronary syndrome in adults and myocarditis in...
children. In such cases, a coronarography does not visualize changes in the coronary arteries.

**ETIOPATHOGENESIS**

The pathomechanism of neurogenic stunned myocardium has not been fully elucidated. It was once assumed that the condition resulted from ischaemia of the myocardium caused by the contraction of epicardial coronary vessels and microcirculation disorders. Currently, it is believed that the most likely cause of NSM changes is catecholamine-induced myocardial damage [2, 3, 22]. Increased blood concentrations of circulating catecholamines are considered less important and the role of increased local noradrenergic neuronal activity is highlighted [3]. Damage to the insular cortex and hypothalamus leads to the increased release of catecholamines from the sympathetic nerve endings, which results in local toxic effects on the myocardium. Excessive local stimulation of postsynaptic receptors causes the prolonged opening of β1 adrenergic receptor-dependent calcium channels [3, 24]. This prolongs actin-myosin interactions resulting in the depletion of ATP stores and mitochondrial dysfunction [27]. Another consequence of calcium inflow to the cells is the release of free oxygen radicals and peroxidation of cell membranes, due to which some cardiomyocytes die. This can be visualized histopathologically as myocardial contraction band necrosis, i.e. focal myocytolysis without ischaemic necrosis, myofibrillar degeneration and the formation of irregular transverse bands. Moreover, excessive contraction of sarcomeres and interstitial infiltration of lymphocytes and monocytes are observed. The histopathological lesions are most profoundly expressed subendocardially while the apex is relatively spared; their severity correlates with sympathetic innervation and not vasculature [27]. Another contributing factor to NSM may be excessive peripheral activity of the sympathetic system with increased concentrations of circulating catecholamines. According to monkey experimental model findings, myocardial sympathetic denervation, as opposed to vagotomy or bilateral adrenalectomy, completely eliminates the phenomenon of subendocardial necrosis [3], which confirms the role of local release of catecholamines from nerve endings. Moreover, animal studies demonstrate a correlation between concentrations of troponin I, CK-MB and catecholamines in plasma [13]. The theory described above seems to be confirmed by a small-scale study involving patients with subarachnoid haemorrhage in whom the administration of propranolol and phentolamine had cardioprotective effects [13]. Likewise, another randomized study of 114 patients with acute CNS damage has demonstrated that the immediate initiation of atenolol treatment reduced the severity of myocardial necrosis determined by increased CK-MB concentrations [13]. The question arises whether catecholamines commonly used in such cases can exert iatrogenic effects. Further studies comparing catecholamines with other drugs supporting circulation via a different mechanism, e.g. vasopressin, are required in order to answer this question.

Furthermore, the parasympathetic system seems to play some role in the development of NSM, mainly by modulation of the inflammatory response induced by acute CNS pathology (e.g. subarachnoid haemorrhage or cerebral stroke) [3, 27]. The acute pathological process in the CNS results in an enhanced inflammatory response. Immunologically active mediators, including cytokines, adhesive molecules, biologically-active peptides and others, are produced in the brain and released into the systemic circulation [27]. This can initiate systemic inflammatory response syndrome (SIRS), leading to the dysfunction of many organs, including the heart [27]. Stimulation of the descending fibres of the vagus nerve inhibits the inflammatory response and thus can limit heart injury [32]. The precise anti-inflammatory mechanism seems to result from acetylcholine effects on αbungarotoxin-sensitive nicotinic receptors on tissues macrophages, which inhibit their release of cytokines, e.g. TNF, IL-1 and HMGB1 (proteins of high-mobility group box) [3, 29]. Therefore, parasympathetic system dysfunction and excessive sympathetic activation lead to an uncontrolled inflammatory response in the myocardium and its resulting damage [27, 32].

**NEUROGENIC STUNNED MYOCARDIUM, TAKOTSUBO CARDIOMYOPATHY AND THE REMAINING STRESS-INDUCED CARDIOMYOPATHIES**

Takotsubo cardiomyopathy was first described by Hi-karu Sato in Japan in 1990 in a patient with clinical and electrocardiographic manifestations of acute myocardial infarction, yet without any coronaryographic atherosclerotic lesions [5]. A ventriculography revealed the characteristic shape of the left ventricle with dyskinetic dilatation of the apex and narrowing of the medial ventricular part; hence the name “takotsubo” was suggested, which in Japanese means an octopus trap with a narrow neck and a round bottom. The syndrome has been most commonly described in postmenopausal women (80–100%), as a result of emotional stress. The diagnostic criteria suggested by the Mayo Clinic include transient akinesia or dyskinesia in the left ventricular mid-segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; frequently, but not always, a stressful trigger; the absence of obstructive coronary disease; new ECG changes (elevation of ST segment or negative T waves); the lack of recent head trauma, intracranial haemorrhage, pheochromocytoma, myocarditis, and hypertrophic cardiomyopathy [15].
It has been suggested that NSM and Takotsubo cardiomyopathy represent, in fact, the same syndrome of a slightly different clinical manifestation [6], which is confirmed by numerous similarities in the clinical picture and in etiopathogenesis. It is assumed that both are induced by catecholamines and their incidence is higher in women. They are associated with left ventricular contractility impairment without changes in coronary vessels. The ECG findings often reveal changes mimicking myocardial ischaemia; moreover, in both syndromes blood concentrations of markers of myocardial injury are elevated. The differences that are fundamental for their differentiation as two separate pathologies include segmental contractility disorders predominantly affecting the apex in Takotsubo cardiomyopathy and global contractility disorders in NSM. A very logical concept has recently been put forward that all stress-related cardiomyopathies, i.e. NSM, Takotsubo cardiomyopathy, critical conditions-related cardiomyopathy, transient cardiomyopathy in pheochromacytoma and induced by exogenous catecholamines, have a common pathomechanism and represent a clinical spectrum of the same syndrome [2]. This theory is confirmed by numerous similarities in their clinical picture as well as a common catecholamine-mediated pathological mechanism. Transient cardiomyopathy of critical conditions affects mainly patients treated in intensive care units, most commonly (up to 50%) due to sepsis, followed by patients treated due to acute pulmonary disease. Contractile dysfunction can involve the entire left ventricle, apical or mid-segmental hypokinesia and isolated hypokinesia of the apex or the anterior left ventricular wall [2]. In cardiomyopathy related to pheochromacytoma, global contractility impairment is usually observed, although in some cases the apical part is spared or otherwise mostly involved, as in Takotsubo cardiomyopathy. The fact that cardiomyopathy usually does not develop in cases without adrenal crisis confirms its cause-and-effect relationship with an excess of catecholamines [2]. Case reports of transient cardiomyopathy in individuals receiving β-receptor stimulating drugs due to asthma or exacerbations of chronic obstructive pulmonary disease, as well as in patients administered intravenous or subcutaneous adrenaline, have also been published [2].

**TREATMENT**

As NSM syndrome has been described only recently, there are no clear guidelines for its management. It is generally believed that treatment directed at the acute cerebral injury underlying NSM is essential [3]. Early monitoring of patients with acute neurologic syndrome, particularly following a cerebral stroke, is of great importance. Continuous ECG monitoring, assessment of left ventricular function (ECHO) and determinations of biochemical markers of myocardial injury are necessary [3]. Symptomatic treatment is generally recommended: drugs improving myocardial contractility, catecholamines, phosphodiesterase inhibitors and typical management of arrhythmias are applied. Since NSM syndrome can be induced or enhanced by catecholamines, as described earlier, it seems that phosphodiesterase inhibitors, e.g. milrinone alone or, as a last resort, combined with dobutamine are more beneficial [16]. Taking into consideration NSM pathophysiology, particularly in severe cases, treatment with levosimendan would be indicated. Indeed, its triple mechanism of inotropic action is independent from adrenergic receptors. Firstly, it involves the sensitization of cardiomyocytes to calcium ions by binding the subunit of cardiac troponin C. Secondly, it activates ATP-dependent kalium channels, which additionally provides vasodilating action and last, but not least, inhibits selectively phosphodiesterase III (PDI III), particularly in higher doses. Unlike catecholamines, levosimendan does not increase myocardial oxygen demands and exerts cardioprotective effects. To date, one case of effective levosimendan treatment of NSM following subarachnoid haemorrhage has been described [16].

Attempts have also been made to use β-blockers in NSM treatment, in an attempt to reduce the severity of changes induced by catecholamines [16]. Some authors recommend the early consideration of β-blocker therapy in patients with subarachnoid haemorrhage due to the highest risk of ventricular arrhythmias at this stage [2]. Indeed, a paper published most recently confirms that the risk of NSM is lower in patients with subarachnoid haemorrhage treated with β-blockers [7].

Considering the potentially adverse, iatrogenic effects of catecholamines in stress-induced cardiomyopathies, some alternative treatment methods of associated low cardiac output syndromes must be sought, e.g. the inotropic use of insulin [8]. Recently, the cases of effective NSM treatment with the infusion of insulin have been described [18, 19]. Moreover, some patients can benefit from the use of intra-aortal balloon counterpulsation [9].

A different therapeutic problem involves patients with brain stem death due to CNS damage qualified for organ donation. As hypotension is common, catecholamines are infused to ensure proper organ perfusion. It is estimated that about 20–40% of potential heart donors have been rejected due to global or segmental impairment of left ventricular contractile function. In some of these cases NSM syndrome could possibly have been diagnosed, which is potentially reversible. We should therefore look for reliable methods to predict the reversibility of left ventricular dysfunction, as they are currently unavailable. Thanks to such methods, the pool of hearts for donation would increase without any risk for recipients. There is a theoretical risk of iatrogenic myo-
cardiac damage due to catecholamine therapy. Therefore randomised studies comparing the standard catecholamine therapy with other drugs increasing arterial pressure, e.g. vasopressin, should give us new insight along with an evidence-based approach to donor management. Such studies could optimize heart preparation for transplantation, increase the number of transplants, as well as affect positively the function of transplanted organs and the survival of recipients. Despite concerns regarding the potentially adverse effects of catecholamines in NSM syndrome, clinicians still find them an important element in the treatment of acute left ventricular failure, even in NSM, until alternative methods of treatment are found to be more beneficial.

SUMMARY

Neurogenic stunned myocardium syndrome has to be considered in the differential diagnosis of acute heart failure in individuals with acute CNS pathology. Early monitoring is crucial for clinicians, which enables one to detect developing circulatory disorders. It seems that patients with acute neurologic abnormalities should be provided with routine cardiologic screening involving ECG and ECHO monitoring, possibly also cardiac enzymes and markers of injury, which could help with early diagnosis and treatment of NSM and facilitate the evaluation of its actual incidence. As acute neurologic conditions are less frequent in children than in adults, the data on the incidence of NSM in this population comes from case reports. Therefore, routine monitoring of the cardiovascular function in all such patients should be considered. Further studies are required to broaden our knowledge about the pathomechanisms underlying NSM syndrome and to find the most effective methods of its treatment and prevention. It seems essential to determine the effects of exogenous catecholamines on NSM. Once their negative influence is confirmed, alternative methods of treatment should be sought.

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