Takotsubo Syndrome *versus* Neurogenic Stunned Myocardium

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**INTRODUCTION**

Interrelations between heart and brain were first described by anatomists and physiologists and later by clinicians. In time, the brain-heart interrelation became a major subject in both neurology and cardiology and in the newly derived specialty, neurocardiology.

The great neurosurgeon Cushing noted bradycardia and hypotension in response to increased intracranial pressure during brain interventions, as a remarkable interaction between brain and cardiovascular system.

In 1990, in Japan, Suto et al. published a series of similar cases with clinical features of acute myocardial infarction, but normal coronary angiography, reversible ventricular dysfunction but with a special echocardiographic aspect of “apical ballooning” (1). Such cardiac observations were especially noticed in women aged 55-60, with important emotional stress. The pathological condition was initially named Takotsubo or Takotsubo syndrome (TTS). Numerous publications on TTS described the etiologic conditions, various echocardiographic aspects, electrocardiographic changes and cardiac markers shared by patient groups.

The cardiological and neurological data assembly led to the description of a special type of cardiomyopathy called stress cardiomyopathy (2). In the general acceptance, “stress cardiomyopathy (SCMP)”, “Takotsubo syndrome (TTS)” and “Takotsubo cardiomyopathy (TTC)” have the same meaning. Stress cardiomyopathy could be defined as a syndrome of acute transient left ventricular dysfunction (systolic and diastolic), as a result of a myocardial injury, in most cases accompanying an emotional or physical stress.

Apart from the aspects described for SCMP or TTS, there have been noticed a number of special cardiac aspects with reversible ventricular dysfunction and echocardiographic, electrocardiographic, and cardiac markers changes, after neurological events such as subarachnoid hemorrhage (SAH), cerebral trauma, ischemic or hemorrhagic stroke. Cardiac manifestations are partly similar to TTC, with some particular features. This new pathological condition was named “neurogenic stunned myocardium” (NSM), to emphasize the essential physiological change (3).
In the view of these new data on brain-heart interrelation, there is scientific debate regarding the relationship between TTC and NSM, whether there are distinct entities or a single entity (stress cardiomyopathy), as a result of common and complex physiological changes, implying cerebral structures, sympathetic hyperactivity and hypercatecholamines (3, 4).

This work is a synthetic presentation of the current data on TTC (Takotsubo cardiomyopathy) and NSM (neurogenic stunned myocardium), the common and specific traits, including evolution and prognostic, along with the physiological changes implicated in the brain-heart interrelation.

**Takotsubo cardiomyopathy or Takotsubo syndrome**

The Takotsubo syndrome (TTS) or Takotsubo cardiomyopathy (TTC) is generically defined as a type of acute reversible myocardial injury, characterized by transient systolic dysfunction. In a larger sense, TTC is a clinical syndrome characterized by acute and transient left ventricular (LV) systolic (and diastolic) dysfunction, often in relation with an emotional stress in the preceding days (2). Typically, the regional kinetic abnormality that defines TTC is apical hypokinesia/akinesia/dyskinesia (ballooning) with basal hyperkinesia. Usually, TTC is suspected echocardiographically in a patient presenting with a clinical picture of acute myocardial infarction (AMI).

The exact incidence of Takotsubo cardiomyopathy is unknown, published data underestimating the real incidence. It is frequently mistaken for acute coronary syndrome and it is estimated to represent 1-3% of all STEMI patients, 5-6% for women over 55-60 years of age (5).

Some works classify Takotsubo cardiomyopathy into a primary and secondary form depending on the occurrence of the clinical picture as a primary event or in other critical conditions, mainly cerebral events (1, 2).

Definition criteria for stress cardiomyopathy evolved in the last 10-15 years, as more scientific data gathered. At the beginning, Mayo criteria (2004-2005) were used, the last of which being revised (6). Mayo diagnostic criteria, long used for diagnosing Takotsubo Syndrome, were relatively simple:

1. Systolic dysfunction of the left ventricle (LV) (almost specific localization) that exceeds the distribution area of an epicardial coronary vessel;
2. Absence of obstructive coronary artery disease or absence of angiographic proof of an acutely ruptured plaque;
3. New electrocardiographic changes or modest rise in myocardial troponin;
4. Absence of pheochromocytoma or myocarditis.

Later, in 2006, the American College of Cardiology and American Heart Association classified TTC as a primary cardiomyopathy and ESC elaborated different diagnostic criteria. To date, there is a consensus regarding the stress cardiomyopathy diagnostic criteria, “International Takotsubo Diagnostic Criteria” (Intern. TAK diagnostic criteria) (7). The last detailed consensus document, which is largely used for the clinical diagnostic, is concisely presented in Table 1.

In summary, the current mentioned criteria signal the presence of a myocardial injury with reversible left ventricular dysfunction, but with some elements from the secondary type of Takotsubo syndrome (neurologic events trigger or phochromocytoma).

The main (but not the only) diagnostic criteria for Takotsubo cardiomyopathy are echocardiographic changes. The typical echocardiographic aspect initially described in 75-89% of cases is predominantly apical hypokinesia, akinesia, or dyskinesia (apical ballooning) and basal hyperkinesia, occasionally associated with left ventricular ejection tract obstruction (2, 8). Another echocardiographic type is midventricular circumferential hypokinesia/akinesia (in 10-20% of cases), with normal apical contractility (midventricular ballooning), potentially leading to severe left ventricular dysfunction and acute heart failure. There were described other echocardiographic aspects: a basal type (inversed? Takotsubo), biventricular dysfunction or just right ventricular dysfunction or focal dysfunction (9).

In synthesis, five anatomical variants of stress cardiomyopathy, with different prevalence, were described: apical ballooning (75-80%), midventricular (10-20%), basal or reversed? (5%), biventricular (<5%) and focal dysfunction.
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The different anatomical and echocardiographic variants could be explained by different and high density of beta-adrenoreceptors in various anatomic regions and thus, different effects of the hypercatecholaminemia (1, 2).

The electrocardiographic data show widely distributed myocardial injury; in more than 90% of cases there are suggestive ECG changes. In the typical form, clinical manifestation are those of myocardial infarction and on electrocardiogram there is ST segment elevation in precordial leads (9), followed – in 24-48 hours – by ischemic changes, with reversed T waves, often accompanied by prolonged QT interval, that could progress beyond 500 ms, predisposing to polymorphic ventricular tachycardia or ventricular fibrillation, both also potentially present in STEMI patients. The electrocardiographic characteristic almost specific for stress cardiomyopathy is the ST segment elevation in aVR plus ST segment elevation in anteroseptal leads (115). In such cases with severe left ventricular dysfunction, coronary angiography and ventriculography is recommended to confirm Takotsubo syndrome.

The ST segment depression is rare (less than 10% of cases) and suggests an alternate diagnostic: acute coronary syndrome, neurogenic stunned myocardium or acute myocarditis.

Cardiac biomarkers can also bring definitive elements to diagnose Takotsubo syndrome and to differentiate it from STEMI/non-STEMI or acute myocarditis. Troponins T and I are moderately elevated (conventional or high sensitivity), discordant with the magnitude of electrocardiographic and echocardiographic changes found in studies (1, 2). The troponin dynamic does not show the relatively rapid rise and fall found in acute myocardial infarction. The (systolic and diastolic) ventricular dysfunction, always present in the Takotsubo syndrome, is accompanied by high levels of NTproBNP; the serum level correlates with the degree (extent) of ventricular motion abnormalities (12). The level of BNP or NTproBNP reaches a peak at two days and remains elevated up to three months (12), suggesting the persistence of physiological changes present in Takotsubo cardiomyopathy.

Seric catecholamines show high levels in the first days, higher than for AMI. Seric and regional-myocardial catecholaminaemia plays an essential role in the pathology of Takotsubo syndrome.

Other specific cardiology tests are unnecessary, except for the coronary angiography, indicated in special emergency conditions to exclude an acute coronary syndrome.

Among the first diagnostic criteria for Takotsubo syndrome (Mayo criteria), the absence of either an obstructive coronary artery disease or a ruptured plaque is included, and in the present criteria it is specified that the presence of a significant coronary artery disease is not a contradiction in Takotsubo syndrome, as significant coronary artery disease was found in 10-29% of cases (8, 13), the presence of coronary artery disease not being considered now an exclusion criteria (1). The extent of motion abnormalities that exceeds the territory of a single epicardial vessel pleads for Takotsubo syndrome, especially when coronary angiography did not find critical coronary lesions.

**Evolution and prognostic in Takotsubo cardiomyopathy**

In hospital and long term evolution of Takotsubo cardiomyopathy is related to the degree of ventricular dysfunction and the regression (in one to three weeks) of motion abnormalities. In hospital, mortality is approximately 5%, similarly to that of STEMI. The complicated evolution is related to the arrhythmic risk, evolution towards...
acute heart failure, more rarely systemic embolism (especially in the apical ballooning form) and obstruction of the left ventricular ejection tract (15).

Arrhythmias may be present in up to 25% of patients, especially atrial fibrillation in 5-15% of cases and ventricular arrhythmias in 4-9% of cases (16). High rate atrial fibrillation in the presence of severe left ventricular dysfunction leads to acute heart failure or cardiogenic shock. Ventricular tachyarrhythmias, especially Torsades-de-Pointes, complicate Takotsubo syndrome with more than 500 ms QT interval prolongation, negative T waves and low ejection fraction.

Independent predictors of acute heart failure are, other than reduced left ventricular ejection fraction on admission, high troponin levels, the echocardiographic type with medioventricular dysfunction and right ventricle involvement (1). Mortality for all types of stress cardiomyopathy is up to 5% and is higher in hemodynamically unstable patients with cardiogenic shock or cardiac arrest (17).

Left ventricle dysfunction recovery – especially in the typical form (apical ballooning) in gradual, usually in one to two weeks from the onset, but it is possible as soon as 48 hours or delayed.

Stress cardiomyopathy recurrence has an annual rate of 2-4%. After left ventricular ejection fraction recovery, a degree of fatigue, dyspnoea or low effort capacity may persist.

Long-term evolution of Takotsubo patients was initially considered benign, with a mortality similar to that of normal subjects.

A systematic review and a meta-regression study analyzed the long term evolution on a cohort of >10 000 TTS patients from 54 studies (18) and found an in hospital mortality of 1.8%, similar to that in ACS, a 3.5% mortality on a 28 months follow-up, mainly due to non-cardiac causes and a recurrence rate of 1%.

By using meta-regression analysis, the above-mentioned study identified three factors which were significantly associated with long-term mortality: advanced age, TTC developed by physical stress and cardiac dysfunction not limited to apical ballooning (18).

The numbers for mortality and recurrence are, however, inferior to those found by a recent review (2).

The possible mechanism affecting long term prognosis in TTC and stress cardiomyopathy in general is linked to the contractile dysfunction developed in time by an infiltrative process and the consecutive global myocardial fibrosis.

Neurogenic stunned myocardium

Neurogenic stunned myocardium (NSM) can be defined as an acute and reversible myocardial dysfunction, occurring after different types of neurologic events, with participation of the autonomic nervous system (ANS) (19). Unlike Takotsubo syndrome, that is mainly preceded by a psychological (emotional) stress, especially in women over 55-60 years, NSM follows a defined neurological event, particularly subarachnoid hemorrhage (SAH). Essential, NSM is a type of stress cardiomyopathy like Takotsubo syndrome, with similarities and differences. Some authors consider NSM as a Takotsubo-like or a secondary Takotsubo (as in pheochromocytoma, for example).

NSM incidence after an acute neurologic event varies between 20% and 40%, depending on the type of event; the incidence is higher in SAH (approximately 33% of cases) and cerebral trauma (22%) and lower in other conditions such as ischemic stroke, encephalitis, epilepsy, metastatic tumors and reversible posterior encephalopathy (3, 20).

The severity of NSM depends on the type and severity of the neurologic disease and on involvement of some neurologic structures (insular cortex, hypothalamus, etc).

Diagnostic criteria for NSM are not defined as for Takotsubo syndrome, but include partly common clinical and echocardiographic elements.

The presentation prototype for NSM is that found and described in SAH.

The diagnostic evaluation generally follows the exploration of the Takotsubo syndrome: electrocardiography, echocardiography and cardiac markers.
The electrocardiographic examination finds electrical anomalies in about 90% of patients with SAH, 60-70% of those with brain haemorrhage and 15-30% of those with ischaemic stroke (21). The most frequently encountered ECG changes are as follows: reversed/negative T waves, ST segment depression, QT interval prolongation, large U waves (19).

Arrhythmias may be present, especially in SAH (over 90% of cases) but also in ischaemic or haemorrhagic stroke (20-40%) (19). The most frequently encountered arrhythmias include bradycardia, atrial arrhythmias (atrial fibrillation, flutter) and multifocal ventricular tachycardia (22). The highest prevalence is encountered for atrial fibrillation, frequently silent, in 14% of patients and other supraventricular arrhythmias in 5%. Arrhythmias occur between 2-3 days and one week and can be self-limited or controlled pharmacologically.

The ECG changes are not specific to NSM and their meaning can only be established in the clinical context, together with other investigations (echo, cardiac markers). Data suggest myocardial injury and likely acute coronary syndrome (2).

The echocardiographic exam in NSM detects regional motion disturbances and possibly systolic ventricular dysfunction. Regional motion disturbances are usually in the basal and midventricular segments of the anterior and anteroseptal walls of the left ventricle (20, 21).

Systolic ventricular dysfunction (and/or diastolic), either global or regional, was found in 10-20% of SAH patients (21). Some works noticed a reduction of LVEF < 50% in 55-60% of patients, but only 6.6% of patients had LVEF < 40% (24, 25). Ventricular dysfunction is reversible in a few weeks, but full recovery may take longer. Ventricular dysfunction in NSM patients can be accompanied by acute pulmonary edema and haemodynamic instability down to cardiogenic shock (20); it represents a significant new risk factor in patients who experience an acute neurological event.

Cardiac markers can be moderately increased in NSM, as in the Takotsubo syndrome. The incidence of LcTnI and TnT troponin increase as an effect of myocardial injury ranges in SAH between 20-37% and reaches the threshold level in 24-28 hours (26, 27). In one study, hsTnT > 89 ng/L at 24 hours since SAH occurrence had predictive value for NSM with a sensitivity of 100% and a specificity of 79% (28). High values of troponins would be associated with the development of parietal motion anomalies and would be an indicator of ventricular dysfunction (27). Brain natriuretic peptide (BNP) can also increase in NSM, correlated with regional motion anomalies. Increased BNP values would be significantly associated with diastolic dysfunction, pulmonary edema, troponinaemia and LVEF.

Evolution and prognosis

The evolution and prognosis of cardiac anomalies after neurologic events (injuries) are determined by the severity of the neurologic event and by the degree of ischemic injury of the heart.

NSM-type cardiac changes in SAH occur quickly, during the first two days. Wall motion disturbances and ECG changes diminish during the next 7-8 days (29). In most patients, the stunned myocardium aspect disappears completely, especially when ventricular dysfunction was unimportant. In a meta-analysis on the impact of cardiac changes on prognosis after SAH it was found that motion anomalies, troponin and BNP levels, ST segment depression and T wave anomalies were associated with adverse prognosis, higher mortality and delayed recovery after SAH (30).

Also, the evolution of the neurologic event as well as the type and location of ischemic stroke have a major influence on patient evolution. The risk of non-fatal AMI is of 3.3% in the first three months and 8.2% at five years (31). Left insular stroke is associated with a higher risk of adverse cardiac events compared with other sites (19).

A direct comparison between clinical aspects, ECG changes, location and type of parietal motion changes, the LVEF, evolution and other parameters of the Takotsubo syndrome and NSM was achieved in two important studies (3, 32). A first study was performed in 61 patients with a Takotsubo syndrome and 37 with NSM. The NSM patients were younger (by about 10 years), the prevalence of acute pulmonary edema was higher at admission, while in Takotsubo syndrome the initial manifestations were angina and ST segment elevation. Motion anomalies were mostly apical in the Takotsubo syndrome, while the LV dysfunction was global in NSM patients. The natural evolution of the two groups was si-
similar. The study arrived at the conclusion that both conditions represent the same syndrome of stress cardiomyopathy.

A different point of view results from the second study, of 36 NSM patients and 22 with Takotsubo syndrome (3). Takotsubo syndrome patients presented with angina, while the NSM one did not have signs and symptoms of cardiac ischaemia. About 60% of Takotsubo patients had ST segment elevation, which was not present in any of the NSM patients. The majority of Takotsubo patients (77%) had apical dysfunction and in about 45% of them, the dysfunction involved also mid and basal segments. On the contrary, only 13% of the NSM patients had basal or myocardial dysfunction.

In conclusion, it can be considered that between the Takotsubo and neurogenic stunned myocardium syndromes there are more similitudes than differences. Both have an aspect of reversible myocardium injury with motion anomalies at various sites and modest increases of cardiac markers, the broad picture suggesting a common, neurogenic, pathophysiologic mechanism that has the features of a stress cardiomyopathy with two subtypes: Takotsubo syndrome and neurogenic stunned myocardium.

Pathogenic mechanisms

The pathogenic mechanisms of the Takotsubo syndrome and of NSM are, in part, known from experimental data and clinical research. The many clinical and investigational elements, common in the Takotsubo syndrome and NSM led to the idea of a similar pathogenic mechanism, with different stressor factors.

A simplified schematic of the pathogeny (Figure 1) indicates the emotional and physical stress as inducing factors, followed by sympathetic overstimulation and the activation of specific brain regions (the hypothalamus) (33) and the consecutive release of catecholamines.

Depending on the specific nature of the acute trigger, the dominant sympathetic response can be neural (local, myocardial release of epinephrine) or adrenal with increased release of catecholamines in the bloodstream. Sympathetic hyperstimulation and hypercatecholaminaemia results in myocardial cell involvement through coronary spasm, endothelial dysfunction, involvement of microcirculation, eventually leading to reversible myocardial injury and its components (32).

There are multiple pieces of evidence of the central role of sympathetic activation in the Takotsubo syndrome, arising from different fields.

- In most patients with Takotsubo syndrome (stress cardiomyopathy), an emotional (27%) or physical (36%) initial stress factor is found, that results in a catecholamine storm. However, stress factors can also be minor and associated. In about 30% of Takotsubo syndrome patients there is no identifiable trigger preceding the syndrome (8, 34).

- Pathological conditions due to hypercatecholaminaemia are accompanied of ECG and echocardiographic changes similar to the Takotsubo syndrome. Pheochromocytoma were noticed in 13% of the Takotsubo cases (35) that were thus considered secondary Takotsubo syndromes. Some major neurological events like SAH, haemorrhagic or ischaemic stroke, brain trauma etc are accompanied by hypercatecholaminaemia and NSM (Takotsubo like). Acute stroke that involves the insular cortex is associated with sympathetic hyperactivity, increased level of plasma catecholamines, arrhythmias and BNP (36).

- Acute catecholamine administration (epinephrine, norepinephrine, dopamine) mentioned in research papers, could be a triggering factor for the Takotsubo syndrome (1).

- The plasmatic level of catecholamines is massively increased in most TTS lesions, as in AMI as well as in patient with TTS and pheochromocytoma (37). When plasma catecholamines are not increased, a proposed mechanism was their myocardial increase through local sympathetic stimulation.

- More evidence on the sympathetic pathogenesis of Takotsubo syndrome arise from histopathological exams. Endomyocardic biopsies in TTS did identify lesions with contractions in bands of necrosis and inflammatory infiltrates with mononuclear cells, which is distinct from polymonuclear infiltrates seen in AMI (38). Lesions of the same type have been described in hypercatecholaminaemia, for example in pheochromocytoma, SAH, brain trauma, elements that suggest that catecholamines are an important link between stressor factors and myocardial injury.
In summary, sympathetic hyperstimulation and hypercatecholaminaemia play a central role in the myocardial injury or stress cardiomyopathy. The effects of sympathetic stimulation at the myocardial level would be produced at multiple levels: (1) coronary vasoconstrictions (variable spasm); (2) microvascular dysfunction; (3) direct cardiotoxic effect of catecholamines at myocyte level; (4) secondary involvement of an inflammatory process (1, 32).

Multivascular coronary vasoconstriction was initially considered to be the main pathogenic mechanism. The endothelial dysfunction due to adrenergic stimulation could determine multivascular coronary vasospasm, transitory ischaemia and myocardial dysfunction in multiple territories. Coronary vasoconstriction in epicardial vessels was proven however in only 20% of TTS patients (32). Moreover, there was no proof of experimental coronary spasm with multiple agents.

The type of contractile dysfunction in TTS would necessitate the presence of vasospasm only on some coronary arteries, but actual contractile dysfunction extends beyond the area irrigated by a single vessel. With all these contradictory data, the involvement of vasospasm cannot be excluded in a subset of TTS patients, but it is unlikely that it represents the primary mechanism of myocardial stunning (1).

Sympathetically mediated microvascular dysfunction, through adrenoreceptor and endothelium receptors type A, would represent an important pathogenic mechanism, which is proven by the reduction of the coronary reserve coronary flow both invasively and non-invasively (39). In the acute phase of TTS, intravenous administration of adenosine improves myocardial perfusion, regional motility and LVd (40). Microvascular dysfunction is transitory and its recovery is correlated with the improvement of contractile function.

Microcirculatory dysfunction, which is unequal across the left ventricle, reflects local differences in sympathetic innervation and adrenal receptor distribution. Beta-receptors have a higher density at the base of the heart compared to the apex, and apex receptors are more responsive to sympathetic stimulation (41). This distribution makes them more vulnerable to rapid catecholamine increase and the resulting apical ballooning.

Acute microvascular dysfunction could also be a secondary factor, as proven by bioptic changes that displayed endothelial apoptosis (42).

In summary, endothelial and coronary microcirculation dysfunction, both influenced by neural activity and alpha and beta receptors, results in conditions of myocardial stunning with various types of parietal motility disturbances (43).

The direct toxicity of catecholamines on the myocardium could explain the transitory dysfunction of cardiac motility. Cardiotoxic effects of excess catecholamines have been also found in pheochromocitoma, with local myocarditis lesions. In stress cardiomyopathy, bioptic exams demonstrated necrosis bands, a unique type of myocardial injury that is associated with hypercatecholaminaemia states (44). The mechanism through which hypercatecholaminaemia results in cell injury is the cyclic AMP, that leads to intracellular calcium overload (1).

The role of systemic inflammation was also claimed in the pathogenesis of stress cardiomyopathy. The role of systemic inflammation in the reversibility of myocardial dysfunction has been also described in sepsis cardiomyopathy (45). Also, a systemic inflammatory response was correlated with NSM following craniocerebral trauma (46). Some studies showed increased inflammatory cytokines (TNFα, interleukin in the sera of patients with SAH and NSM) (47).

**CONCLUSIONS**

TakoTsubo syndrome, or cardiomyopathy (TTC) and NSM (neurogenic stunned myocardium) are two types of neurocardiological intercorrelation pathologies. These pathological conditions are characterised by usually reversible disturbances of cardiac wall motility, at various locations, and systolic ventricular dysfunctions, usually due to physical or psychological stress and excess activation of the autonomic nervous system and other cerebral structures such as the insular cortex.

The diagnostic criteria of TTC, as defined by an international consensus, specify the elements that define this syndrome, beyond Mayo criteria. The new criteria include the almost specific wall mobility types, ballooning, the possible presence of common atherosclerotic lesions as well as car-
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Diagnostic criteria for NSM are incompletely defined, but partially similar with TTC; differences consist in triggering by a neurological event, such as SAH or stroke, different sites of regional motility disturbances and prognosis ranging from benign to heart failure.

Differences and similarities for the two myocardial conditions raised the problem of whether they are two different types of pathologies or a single syndrome with two subtypes of stress cardiomyopathy.

The main elements that unite them are the common pathophysiological mechanisms: (1) recent physical or psychological stress and hyper-catecholaminaemia through hyperactivation of the autonomic nervous system; (2) transitory coronary vasospasm in multiple vascular territories; (3) microcirculation involvement; (4) probably an inflammatory process. In the end, these elements result in myocardial injury of a peculiar type, followed by lower wall movement in various regions and left ventricular systolic dysfunction of variable duration.

The two subtypes of stress cardiomyopathy regress quickly, in days or weeks, but can be complicated with severe arrhythmias, heart failure, thromboembolism or sudden death.

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References


detection of stress-induced cardiomyopathy in patients with subarachnoid hemorrhage.


