Takotsubo Syndrome: An Historical Perspective

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For the past 25 years there has been an accelerating stream of literature reports on a pathological entity, called Takotsubo syndrome (TTS) (2,882 items in Pubmed, in response to the MeSH term "takotsubo", as of 4/5/16),[1] a term coined by Sato et al,[2] and Dote and al,[3] when they described in 1990 and 1991 respectively a transient left ventricular (LV) dysfunctional state, which make the angiographic silhouette of the LV in systole of the involved patients to resemble "takotsubo", a wide based, narrow necked Japanese fishing tool used to capture octopuses. These authors attributed TTS to a diffuse coronary vasospasm, since the emerging clinical picture appeared to be of ischemic nature, and the coronary arteries were not occluded, or severely stenotic.[2,3] Although the pathophysiology of TTS remains to date elusive, the overwhelming support from the literature[1] suggests that coronary vasospasm is not at the roots of TTS, although it could be a contributor, if a multi-factorial etiological underpinning is assumed.[4] The original descriptions of TTS are inaccessible to the Western physicians, since they are written in Japanese,[2,3] but after a hiatus of 10 years from those reports, the first article written in English, listed in Pubmed, appeared in 2000, which ushered in the avalanche of accelerating reporting on TTS we are currently experiencing.[1]

The objective of this historical perspective on TTS is not to elaborate on the particulars of this mysterious illness (clinical picture, speculations about the pathophysiology, laboratory testing, management, hospital course, and long-term outcomes), since these can be found in numerous comprehensive treatments on TTS,[1] with a most recently published work elaborating on the "current state of knowledge on TTS".[5] The aim of the present piece is to suggest that if one adopts the operational term "stress cardiomyopathy" or "neurogenic heart disease", instead of TTS, and avoids fixation on the systolic appearance of "takotsubo", on LV angiography or echocardiographic evaluation, "TTS" has been encountered and described in various forms, long time ago, starting at the turn of the 20th century. Indeed, even long before that, during the Biblical, ancient Greek and Roman times, a rudimentary notion that strong negative or even positive emotions could harm the heart and result in illness or even lead to death, existed and had been documented,[6] or had been part of the folklore wisdom. Indeed the cases described by Engel,[6] and in his article's 89 references, that led to sudden death, are very similar to the emotional upheavals of patients who presented with TTS.[1] Along this broader conceptualization of TTS, one could consider strong emotions-, or physical stress-triggered death, including sudden cardiac death (SCD), and other preclinical or laboratory expressions of heart disease in the presence of acute illnesses of various body organs, particularly the brain, as TTS phenotypes. It is conceivable that such TTS phenotypes are common, could range from mild[7] to severe and life-threatening, and may be present as comorbidities to other well characterized illnesses.[8]

In his landmark paper published in 1942, entitled "Voodoo death", the eminent Harvard physiologist Walter B. Cannon elaborated on the capacity of the brain's powerful emotions, associated with fear or rage, to harm the heart and result in death, in the absence of any injuries or intercurrent illnesses.[9] His account was meticulously documented to exclude other plausible causes, which could have resulted in the demise of the involved subjects. Cannon postulated that death had been caused "by a lasting and intense action of the sympathico-adrenal system",[8] not different from the contemporary views about the mechanism underlying TTS mediated by an intense noradrenaline stimulation of the heart exerted by the autonomic nervous system,[10,11] and/or by a flooding of the blood stream with catecholamines, generated by the resultant nerve stimulation's overspill, and the adrenal secretion of adrenaline.[12]

Samuels in a comprehensive review of the "neurogenic heart disease", which comprises the heart-specific affliction of a broad pathological spectrum of neurovisceral damage, resulting in the so-called psychosomatic illnesses,[11] summarizes laboratory animal experimentation and clinical work conducted in the past century focusing on cardiac pathologies resulting from spontaneous or intentional overstimulation of the autonomic nervous system (ANS). Indeed extreme heart failure or sudden death in contemporary subjects does occur, in the setting of powerful unbridled ANS stimulation,[10] and it has not been only confined to the aborigines, as Cannon thought.[9] On reading these scientific reports from the animal laboratory or the clinic,[11]

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dating back all the way to 1907,[13] one is left with the notion that the underlying pathology (induced or spontaneously occurring) involved, is not different from what is currently described, and dubbed as "TTS".[1] Accordingly, the aforementioned review[11] references 45 papers which provide insight that:

1) sudden death can strike in patients in psychological distress;[6]
2) experiments on animals kept in confinement result in a high rate of death,[14] reminiscent of more recent work with animal immobilization leading to TTS;[15]
3) both the sympathetic and parasympathetic ANS are involved in the mediation of sudden death, with the latter playing its role later in the course of cerebral hyperactivity;[6,10,14]
4) the dominant mechanism of SCD has a brain hemispheral representation, different for the sympathetic (left insular cortex) and parasympathetic (right insular cortex) ANS in humans, opposite to what has been observed in the rat brain;[16]
5) ECGs from patients admitted with symptoms suggestive of myocardial infarction, proven not to be the case, or had ischemic strokes or subarachnoid or cerebral hemorrhage, revealed "ischemic ST/T changes, and upright and inverted T-waves, with QTc prolongation, occasionally associated with bradycardia,[17-20] reminiscent of patients with the subacute phase of the inverted TTS[11,21] and classic apical/midventricular TTS,[1] respectively;
6) the above ECG changes were associated with cardiac symptomatology in a few patients without evidence of myocardial infarction at autopsy, and were attributed by some to electrolyte disturbances,[19] or by others to lesions in the Brodmann area 13 of the orbital surface of the frontal lobe and area 24 on the anterior cingulate gyrus of the brain;[20]
7) the concept of visceral organ injury, including cardiac lesions, resulting from nervous system disease has been advanced by Ivan Pavlov and Hans Selye, with the latter emphasizing the influence of physical and emotional stress, the nonspecificity of stresses (distress and eustress), the difference of the resulting cardiac lesions from the ones seen in myocardial infarction, modulating effect of fluorocortisol, the primary role of direct sympathetic nervous system (SNS) intense stimulation of the heart, as opposed to the blood-borne catecholamines secreted by the adrenals, and the lack of prevention of cardiac lesions with adrenalectomy;
8) the protective effects of "drugs with direct or indirect antiadrenergic properties: reserpine, guanethidine (catecholamine depletion), mecamylamine (ganglionic blockade), chlorpromazine (inhibition of sympathetic-stimulating reflexes at the hypothalamic level), and dibenaminc (blockade of circulating catecholautines)" for development of structural cardiac lesions was shown in rats, exposed to norepinephrine injections and immobilization and cold stress;[22]
9) the catecholamines released locally into the heart by the autonomic neural connections are much more cardiotoxic, than the ones present in the bloodstream;[22]
10) the combination of the above 2 sources of catecholamines can exert a synergistic cardiotoxic effect;[22]
11) chronic prolonged intracoronary infusion of epinephrine in dogs led to the induction of electrocardiogram ischemic-like (ECG) changes found in patients with neurological pathology, in the absence of ischemic lesions at autopsy;[23]
12) A large number of sophisticated animal experiments implementing electrical stimulation of various anatomic regions of the brain (hypothalamus, insular cortex, cerebral ventricles, and brainstem) induced ischemic-like ECG changes, alterations in heart rate, arrhythmias, and cardiac coagulative myocytolysis, also called myofibrillar degeneration, or contraction band necrosis; [24-26]
13) the above experiments revealed the mediation of both sympathetic and vagal influences on the noted changes;[24,25]
14) spinal cervical 2 section and bilateral vagotomy inhibited the sympathetic and parasyphathetic influences of brain stimulation;[24]
15) b-blockade had an inhibitory effect on the changes induced by cerebral stimulation;[25]
16) the thalamus and insula comprise viscerotropic (not only cardiac) anatomic representations;[26]
17) ample experimental and clinical work, pertaining to a wide range of neurological pathologies, has linked insular cortex and a multitude of other brain sites, to cardiac and lung injury, and sudden death;[27,28]
18) modest rise in cardiac troponins is common in patients with strokes;[28]
19) b-blockade or regional sympathetic blockade of the stellate ganglions may be cardioprotective in patients with strokes;[28]
20) clinical and experimental work spanning the time period between 1964 to 1972,[29-35] revealed an association of neurological (subarachnoid and intracerebral hemorrhage,epilepsy, meningitis, cerebral infarction, and intracranial masses) and psychiatric illnesses, with subendocardial myocardial lesions;
21) caution was advised in using catecholamines in neurosurgical patients, in order to avoid inducing myocardial injury;[30]
22) myocardial lesions in patients with intracranial hemorrhage and midbrain reticular formation stimulation experiments in cats, were most severe adjacent to intramyocardial adrenergic nerve endings;[31]
23) Q-waves in the ECG suggestive of acute myocardial infarction, arrhythmias and ischemic looking ECG changes were seen in patients who died of a subarachnoid hemorrhage and midbrain reticular formation stimulation experiments in cats.;[31]
24) norepinephrine is probably the neurotransmitter mediating locally the cardiomyocyte injury with autonomic sympathetic intense drive;[31]
25) experimental intracranial haemorrhage in normal untreated mice led to myocardial damage, while pretreatments with reserpine, atropine, or adrenalectomy reduced the incidence of myocardial damage from intracranial haemorrhage;[32]
26) the effect of atropine in reducing the myocardial injury consequent to the intracranial haemorrhage was felt to be due to a reduction of a rebound sympathetic activity, although parasympathetic influence is not totally discounted;[32]
27) intravenous noradrenaline (not adrenaline), and subarachnoid hemorrhage produce similar ECG changes in canine experiments;[33]
28) hyperkalemic-like ECG T-wave changes early and ischemic-like T-wave inversions later are seen with both noradrenaline injections and subarachnoid hemorrhage, with the latter associated with irreversible myocardial lesions, when amounts of injected noradrenaline are large, or effect of subarachnoid hemorrhage is prolonged;[33]
29) experimental subarachnoid and intracerebral hemorrhage in mice resulted in myocardial lesions, which were prevented by reserpine pretreatment for 2 weeks;[34]
30) the focal distribution of the myocardial lesions in mice with experimental subarachnoid and intracerebrral hemorrhages seemed to follow the random distribution of norepinephrine-releasing nerve fibers adjacent to the cardiomyocytes;[34]
35) it is conceivable that the myocardial lesions produced under intense sympathetic adrenergic stimulation is due to maximally augmented metabolic rate outstripping the coronary blood supply, and thus may be ischemic in nature;[34]
36) focal myocardial lesions were found in mice with experimental subarachnoid hemorrhage, that was prevented by treatment with subcutaneous propranolol 3 times a day, starting 30 minutes prior to the production of the subarachnoid hemorrhage;[35]
37) the degree of neurological injury, as assessed by the Hunt-

Hess grade in patients after subarachnoid hemorrhage, is a strong independent predictor of associated myocardial necrosis, as expressed by the cardiac troponin release;[36]

38) blood borne epinephrine and norepinephrine did not correlate with cardiac troponin release in patients with subarachnoid hemorrhage, suggesting that a "direct release of toxic levels of catecholamines into the myocardium by the cardiac sympathetic nerve terminals is a more likely cause of neurocardiogenic injury than is adrenal release of catecholamines into the systemic circulation";[36]
39) coagulative myocytolysis,[37] in which the cardiomyocytes die in a hypercontracted state is found in "stone hearts", transplanted hearts, hearts of animals and patients who died suddenly, or were exposed to toxic levels of catecholamines, or suffered severe neurological or psychiatric illnesses;[11]
40) the large variety of sudden unexpected death syndromes appear to have a common neurological explanation, based on the intimate connection of the neurological and cardiopulmonary systems;[10]
41) the neurogenic ECG abnormalities improve when brain death supervenes, thus leading to the disconnection of the brain from the heart;[11]
42) such brain-heart disconnection is also seen in association with severe autonomic neuropathy in diabetes mellitus,[11] and is probably the reason that the prevalence of this disease is low in patients with TTS;[38]
42) brain-heart disconnections are expected to manifest in cardiac transplantation, amyloidosis, and stellate ganglionectomy for management of the long QT syndrome, conditions expected to ameliorate or prevent neurocardiac injury;[11]
42) patients with stroke have a high prevalence of ECG abnormalities , some of which are due to neurogenically mediated myocardial injury;[39]
44) epinephrine infusions could cause cardiac hypertrophy and ECG abnormalities;[13]
45) patients with pheochromocytoma, stroke, which is characterized by elevated blood catecholamines, also have ECG abnormalities and evidence of myocardial injury;[11]
46) myocardial injury is less pronounced a short distance from the myocardial nerve endings than in cardiomyocytes close to the nerve ramifications, implying that the neurocardial damage is mediated by the norepinephrine release from the nerve endings,[33] and not the blood borne catecholamines;
47) coagulative myocytolysis is seen in a large variety of cardiac syndromes, in addition to neurogenic heart disease, like e.g., cardiac reperfusion injury, and is characterized by death of cardiomyocytes in a hypercontracted state, and early calcification, a complex interaction at various cellular function levels between calcium and catecholamines, and development of myocardial lesions without narrowing or obstruction of coronary arteries[40,41], in contrast to coagulation necrosis, seen in the setting of acute myocardial infarction;[37]
48) a large variety of stresses, occasionally in the presence of certain steroids (e.g fluorocortisol), are at the roots of the neurovisceral injury to the cardiomyocytes driven by certain brain loci;[42]
49) sudden unexpected death, resulting from a physical assault, but with absence of internal injuries, is linked to myocardial coagulative myocytolysis, cardiac arrhythmias, and considered similar in pathogenesis to the death suffered by experimental animals under stress; [43]
50) the myocardial histopathologic changes consistent with myocardial coagulative myocytolysis has a predilection for the endocardium, the site of the heart's electrical conduction system, explaining the propensity of victims of TTS to develop heart blocks and cardiac arrhythmias;[11]
51) the concentration of catecholamines was found to be variable in different sites of the canine heart, with a gradient between the apex and base of the left ventricle,[44] which may have a relevance in the appearance of the distribution of the transient left ventricular contraction abnormalities (LVCA) in patients with TTS;
52) the distribution of b-adrenergic receptor subtypes in cardiomyocytes, and conductance and resistance coronary vasculature, in feline and canine experiments varies,[45] which may have relevance for the pathophysiology (cardiomyocyte and/or vascular in nature) of human TTS;
53) the issue of whether cardiac arrhythmias can be initiated and maintained in patients with minor/modest cardiomyocyte injury in TTS, which does not lead to heart failure or detectable LVCA, but still lead to sudden unexpected death is of paramount importance and needs immediate attention;[10,11]
54) the similarity of the lesions to the heart and the gastrointestinal system, produced by hypothalamic stimulation, and the ones emerging during physical or emotional stress or infusion of catecholamines, provides a strong evidence of a common pathophysiologic link between the brain and neurovisceral injury;[46-49]
55) blood-borne catecholamines can intensify the ECG and histopathological cardiomyocyte changes in a variety of experimental models and human stress cardiomyopathy, but they are not essential to their production, leaving the primacy of autonomic nervous system direct stimulation of the heart as the real culprit undisputable;[11]
56) serious cardiac arrhythmias, often with fatal outcome, of neurogenic origin can be induced with reversible mild cardiomyocyte membrane or cytoplasmic derangement, which can even be undetectable by light microscopy;[11]
57) great similarities have been detected in stress cardiomyopathy and reperfusion injury of all kinds, with common pathophysiologic accompaniment of calcium entry following of a period of deprivation; [11,49]
58) the molecular underpinnings of the difference in continuous ischemic injury and reperfusion injury in transmission electron microscopy, and the occurrence of apoptosis in the latter, may have importance relevance for the pathophysiology of TTS;[50]
59) the importance of release of nonerinephine to the injury of only adjacent cardiomyocytes has pathophysiologic relevance for TTS;[51]
60) the influx of calcium and efflux of potassium in stress cardiomyopathy probably explains the peaked T-waves seen early in the course of TTS;[33]
61) the pivotal role of norepinephrine presence in large amounts in neurocardiac excitation in keeping the calcium channels open, with continuous actin and myosin filaments interaction, may have great relevance in the pathophysiology of TTS;[11]
62) the important role of free radicals in stress cardiomyopathy and reperfusion injury, undersores the pathophysiologic similarities of these 2 entities, and the promise of possible means of amelioration;[52,53]
63) the appreciation of the existence of a histopathological continuum of myocardial lesions should be kept in mind to comprehend the variation of clinical outcome (heart failure vs cardiac arrhythmias or sudden unexpected death), imaging phenotypes, release of cardiac biomarkers, seen in TTS, and reperfusion injury;[11]
64) the therapeutic relevance of some interventions, aimed at preventing or ameliorating the cardiotoxic influence of free radicals or calcium overload [52,53] needs to be extended to human TTS, after being implemented in animal experimental models of stress cardiomyopathy.

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This wealth of information, briefly summarized above, and based almost exclusively in the references provided in a key comprehensive review,[11] is rarely quoted in the contemporary literature on TTS. All this experimental and clinical work spans the time of scientific activities of over a century, and has been published prior to the description of TTS as unique clinical syndrome,[2,3] and considered at that time as new pathophysiologic entity. It appears that it may be of immense value to revisit this goldmine of past scientific accomplishments, and study its contents, while we are reading the current literature on TTS,[1] in our effort to unravel the pathophysiology and the management of this mysterious disease.

Declarations of interest

The author declares no conflicts of interest.

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The author states that he abides by the "Requirements for Ethical Publishing in Biomedical Journals".[54]

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