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Review

Contemporary review on the pathogenesis of takotsubo syndrome: The heart shedding tears
Norepinephrine churn and foam at the cardiac sympathetic nerve terminals

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ABSTRACT

Takotsubo syndrome (TS), an increasingly recognized acute cardiac disease entity, is characterized by a unique pattern of circumferential and typically regional left ventricular wall motion abnormality resulting in a conspicuous transient ballooning of the left ventricle during systole. The mechanism of the disease remains elusive. However, the sudden onset of acute myocardial stunning in a systematic pattern extending beyond a coronary artery territory; the history of a preceding emotional or physical stress factor in two thirds of cases; the signs of sympathetic denervation at the regions of left ventricular dysfunction on sympathetic scintigraphy; the finding of myocardial edema and other signs consistent with (catecholamine-induced) myocarditis shown by cardiac magnetic resonance imaging; and the contraction band necrosis on histopathological examination all argue strongly for the involvement of the cardiac sympathetic nervous system in the pathogenesis of TS. In this narrative review, extensive evidence in support of local cardiac sympathetic nerve hyperactivation, disruption and norepinephrine spillover causing TS in predisposed patients is provided.

1. Introduction

Takotsubo syndrome (TS), also known as "broken heart syndrome", neurogenic myocardial stunning [1] or cardiac sympathetic disruption syndrome [2], is an increasingly reported acute cardiac disease entity. The disease is characterized by a clinical presentation resembling that of acute coronary syndrome (ACS). TS is distinguished by a unique pattern of systematized circumferential, typically regional, left ventricular wall motion abnormality (LVWMA) resulting in a conspicuous left ventricular ballooning during systole and extending beyond a coronary arterial territory. The LVWMA is reversible with complete resolution of the left ventricular dysfunction within days to weeks. The ballooning pattern of the left ventricle may be localized to the apical, mid-apical, mid-ventricular, mid-basal, and basal regions of the left ventricle; focal and global involvement of the left ventricle have also been described, the right ventricle may also be involved [3–5]. The term Takotsubo was introduced in 1990 to describe the silhouette of the left ventricle during systole, which resembles a Japanese Octopus pot, in patients presented with a clinical picture of myocardial infarction and normal coronary arteries [6,7]. The disease may be preceded by an emotional stress factor, hence the term "broken heart" syndrome [8]. A myriad of physical stress factors may also trigger TS [3]. The pathogenesis of TS remains controversial. In this narrative review, extensive evidence in support for the involvement of sympathetic nervous system with local cardiac sympathetic hyperactivation – disruption and norepinephrine spillover causing TS in predisposed patients is presented.

2. Pathogenesis of takotsubo syndrome

In addition to the potential role of the sympathetic nervous system and the local cardiac sympathetic nerve terminal [9] in causing TS, several other mechanisms have been debated in the pathogenesis of TS (Table 1). These include: 1) coronary ischemia caused by multi-vessel coronary spasm [10], aborted myocardial infarction in a long wrap-around left anterior descending artery (LAD) [11], coronary microvascular dysfunction [12], and myocardial bridging of LAD; 2) blood-borne catecholamine caused myocardial toxicity; 3) epinephrine-induced switch in stimulus trafficking in β2 adrenoreceptors [13]; 4) left ventricular outlet tract obstruction; and 5) excessive transient ventricular after-load induced by a catecholamine surge [14]. Evidence challenging the above-mentioned competing five hypotheses are vast [2] and are discussed in brief. The findings, which argue against the coronary ischemic hypothesis are: 1) the ongoing chest pain, ST-elevation myocardial infarction (STEMI)-like ECG changes and the absence of coronary spasm or coronary culprit lesion explaining the whole observed LVWMA; 2) the extensive LVWMA and modest elevation in myocardial

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infarction biomarkers; 3) the LVWMA extending beyond the coronary artery supply region; 4) the mid-ventricular or basal localization of TS, which do not match an epicardial coronary artery distribution; 5) the absence of a difference in the prevalence of myocardial bridging in patients with TS, other myocardial infarction with non-obstructed coronary arteries and control groups [15]; 6) the temporal pattern of TS is distinct from those of an acute coronary syndrome [16]; and 7) the histopathological changes of vacuolization and contraction band necrosis, findings, which are not consistent with myocardial infarction. Furthermore, the induction of TS with dobutamine, which has a vasodilatory effect, argues against the microvascular spasm hypothesis [17].

The systematic regional and circumferential involvement of the myocardial segments; the findings of normal or near normal plasma catecholamines in the majority of patients with TS [18–20] and the only modest elevation of myocardial infarction biomarkers argue against blood-borne catecholamine-induced wide-spread myocardial cell necrosis. Indeed some studies [21] have demonstrated no association between the levels of circulating catecholamines (epinephrine and norepinephrine) and myocardial dysfunction in patients with subarachnoid hemorrhage, which is a well-recognized trigger factor for TS. The above findings and the apical sparing subtypes of TS in almost half of the patients with pheochromocytoma induced TS [22] or TS triggered by epinephrine administration [23] challenge both the epinephrine-induced change in "signal trafficking" hypothesis [13] and LVOT obstruction hypothesis. Moreover, the right ventricular wall motion abnormality that may occur in patients with TS cannot be explained by LVOT obstruction [24]. A left intraventricular pressure gradient hypothesis also does not provide a reasonable explanation for the basal and midventricular variants of TS [25,26]. Furthermore, the majority of patients with TS have no demonstrable LVOT obstruction. One recent hypothesis for TS pathogenesis describes "excessive transient ventricular afterload induced by catecholamine-induced left ventricular dysfunction" [14]. The hypothesis puts forward that the administration of vasoconstrictor stimulus causes high afterload and induces inverted or basal TS while the vasodilator stimulus that reduces peripheral vascular resistence lowers systolic blood pressure and ventricular after load were more likely to cause apical ballooning. As mentioned earlier, the majority of patients with TS has normal or near normal plasma and urine catecholamines [18–20]. Moreover, exogenously administered epinephrine in clinical practice may trigger both apical and basal TS [23]. In a recent review of 33 patients with epinephrine-induced TS [27] 42% of cases had apical ballooning and 33% had basal ballooning. However, it should be emphasized that an acute coronary ischemic episode [28–30], hypercatecholaminemia (for example in pheochromocytoma [22,31,32]) and epinephrine administration [23] may each act as a trigger factor for inducing TS. Furthermore, myocardial microvascular dysfunction, epicardial coronary spasm and increased catecholamine may be epiphenomena associated with the diseases that have triggered TS [33]. The LVOT obstruction observed in some patients with TS is most likely a complication rather than the underlying cause of the wall motion abnormality; El Mahmoud et al. [34] in a study of 32 patients with TS demonstrated a relatively high prevalence of LVOT obstruction (25%).

On the contrary, the evidence supporting the involvement of the sympathetic nervous system and the local cardiac sympathetic nerve terminal in the pathogenesis of TS is more robust and discussed in detail in this manuscript.

Table 1
The debated pathogenetic mechanisms underpining takotsubo syndrome.

1- Coronary ischemia
   a. Multi-vessel coronary spasm
   b. Aborted infarction in a long wrap-around left anterior descending artery
   c. Coronary micro-vascular dysfunction
   d. Myocardial bridging
2- Blood-borne catecholamine induced myocardial toxicity
3- Epinephrine-induced switch in signal trafficking (stimulus trafficking) in B2-adrenoreceptiors
4- Left ventricular outlet tract (LVOT) obstruction
5- Excessive transient ventricular after-load induced by catecholamine
6- Cardiac sympathetic hyper-activation, disruption and norepinephrine spillover

3. The sympathetic nervous system in the pathogenesis of takotsubo syndrome

The word "sympathy" signifies the emotional feeling of pity or sorrow for the distress of another. In physiology the same word denotes a relation between parts or organs by which a disease or disorder in one induces an effect in the other, that is to say a physical stress factor. In takotsubo syndrome (TS), the trigger factors (emotional or physical), the clinical presentation and course of the disease provides the most appropriate example to describe the word sympathy as in the following clinical heart breaking case reports. A 44-year-old woman [35] experiences acute crushing chest pain after learning that her 17-year-old son committed suicide. A broad segment of her left mid-ventricular myocardium was stunned and ballooned without evidence of acute myocardial infarction. Another history: a 54-year-old man [36] falls down dead while resuscitating his younger 38-year-old brother and the postmortem cardiac histopathology demonstrated fragmented cardiac muscle fibers with contraction bands; literally the heart was broken into pieces. Pondering the history of these two cases, one cannot forbear to think of the involvement of sympathetic nervous system in the pathogenesis of TS. In this manuscript, evidence for the involvement of sympathetic nervous system in TS with hyperactivation and disruption of the local cardiac sympathetic nerve terminals and norepinephrine spillover resulting in myocardial stunning (cardiac cramp) (Fig. 1) and histopathological findings of contraction bands and in some patient catecholamine myocarditis with myocardial edema are provided.

3.1. First: evidence for sympathetic nervous system hyper-activation-disruption in TS

3.1.1. Emotional stressors

The deep mental anguish that arises from bereavement and induces myocardial stunning in an individual reflects the feeling and the degree of sorrow of that individual for the loss of another. This highly argues for the excessive sympathetic stimulation of the myocardium likely mediated via the brain causing TS. Anecdotal histories related to emotional-induced death has been described since hundreds of years [7]. Sir Henry Wotton, who was an English author and diplomat, wrote upon the death of Sir Albert Morton's wife for about 400 years ago "*He first deceased; she for a little tried to live without him, liked it not, and died*" [7]. More than 70 years ago in 1942, the renowned American physiologist Walter B Cannon [37] published a paper entitled "Vodoo death", in which he reported anecdotal experiences, largely from the anthropology literature, of death from fright as death by "bone pointing" in Australia or as breaking "tapu" in New Zeeland. The author described that the cursed individual might die suddenly within 24 h after bone pointing or might inexorably decline during a period of days. The curse could only be reversed by intervention of the relevant sorcerer. Cannon was the first to postulate that the death could be caused by a lasting and intense action of the sympathico-adrenal system [37].

The term "broken heart" was used under circumstances in which life experiences could become pathogenic and capable of causing cardiac damage and death. Rees and Lutkins in 1967 [38] reported on the results of a survey of the death rate among 903 relatives of patients dying in a semirural area of Wales. They found that 4.8% of bereaved close relatives died within a year of bereavement compared with 0.68% of a non-bereaved control group. The greater increase was found among widows and widowers, their mortality rate being 10 times greater than that of the matched controls. After the first year of bereavement mortality