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Review

Acute cardiac sympathetic disruption in the pathogenesis of the takotsubo syndrome: A systematic review of the literature to date☆

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ABSTRACT

Takotsubo syndrome (TS), also known as broken heart syndrome and neurogenic stunned myocardium, is an acute cardiac disease entity characterized by a clinical picture mimicking that of an acute coronary syndrome. The pathogenesis of TS has not been established yet. Among the most often debated pathologic mechanisms of TS are as follows: first, multi-vessel coronary spasm; second, myocardial microvascular dysfunction; third, aborted myocardial infarction caused by transient thrombotic occlusion of a long wrap-around left anterior descending artery; fourth, left ventricular outflow tract obstruction; fifth, blood-borne catecholamine cardiac toxicity; and sixth, cardiac sympathetic disruption and norepinephrine seethe and spillover. The aim of this review is to provide a thorough analysis of the literature data coming mainly from the neurological literature and dealing with the pathogenesis of TS. Substantial evidence challenging the first five hypotheses and arguing in favor of the hypothesis that acute cardiac sympathetic eruption and norepinephrine seethe and spillover is causing TS in predisposed patients is presented.

1. Introduction

Takotsubo syndrome (TS), also known as neurogenic stunned myocardium, is characterized by a clinical presentation resembling that of acute coronary syndrome; a reversible typically regional ventricular wall motion abnormality with a characteristic circular pattern, which is incongruent with the coronary artery supply region; and a coronary angiography showing no identifiable coronary artery culprit lesion to account for the observed regional ventricular wall motion abnormality [1–8]. The term "tsubo" or "takotsubo" was introduced by Sato et al. [1] in 1990 and 1991 to describe the shape of the left ventricle during systole in patients presented with a clinical picture of myocardial infarction and no obstructive coronary artery disease (Fig. 1). Takotsubo is a pot with a round base and narrow neck used in Japan for trapping octopuses (Tako = octopus and Tsubo = pot). In fact, the disease had been reported under different names including currently used terms a long time before 1990 [9–13]. Rees and Lutkins [13] used the term "broken heart" in 1967 when they reported on the results of a survey of the death rate among 903 relatives of patients dying in a semirural area of Wales. A typical case of broken heart syndrome with documented cardiac image of left ventricular ballooning during systole was reported 1986, 4 years before the introduction of the term takotsubo [11]. This case was diagnosed as "acute myocarditis" but "catecholamine myocarditis" could not be excluded. Cebelin and Hirsch [10] in 1980 reported on human stress cardiomyopathy, 10 years before the introduction of the term takotsubo.

The disease has special predilection for elderly menopausal women [14–16]. The condition affects typically the left ventricle (but the right ventricle may also be involved) and may be localized to the apical, mid-apical, mid-ventricular, and basal parts of the left ventricle [16–19] (Fig. 2). Focal and global left ventricular involvement has also been reported [20,21]. The disease may occur in the setting of severe emotional stress, often after the sudden death of a loved one—hence the alternative name "broken heart syndrome" [3,9,22]. Countless physical stress factors ranging from the most severe diseases as subarachnoid hemorrhage (SAH) and sepsis to the most physiological activities as sexual intercourse may trigger the disease [5,6,14–16]. SAH, brain death and other intracranial disease processes are currently well-recognized trigger factors for TS and are among the diseases and injuries, which have provided a great contribution to the understanding of the pathogenesis of TS [2,23–36]. In this report, a systematic review of the literature data coming mainly from the neurological literature and dealing with the pathogenesis of TS, is presented.

2. Pathogenesis of TS

The etiology of TS has not yet been fully elucidated. Among the most frequently debated pathologic mechanisms underlying TS are

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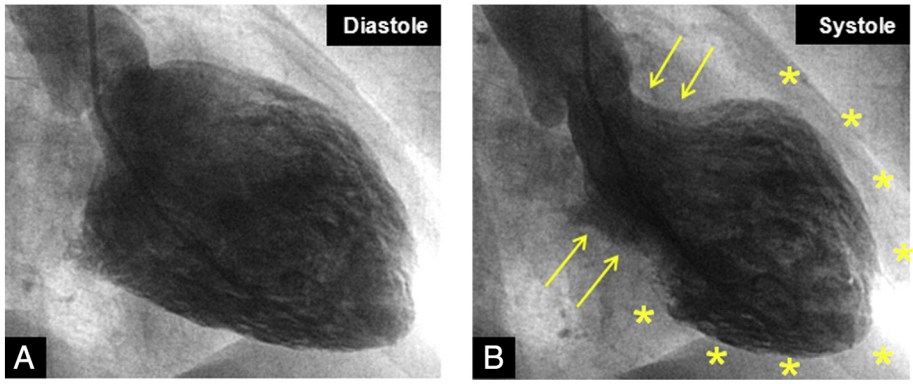

Fig. 1. Left ventriculography in a patient with a classical mid-apical takotsubo syndrome (TS) during systole (A, diastole; B, systole).

the following: first, multi-vessel coronary spasm; second, myocardial microvascular dysfunction; third, aborted myocardial infarction caused by transient thrombotic occlusion of a long wrap-around left anterior descending artery (LAD); fourth, left ventricular outflow tract (LVOT) obstruction; fifth, blood-borne catecholamine cardiac toxicity; and sixth, local cardiac sympathetic disruption and norepinephrine seethe and spillover (a state of extreme sympathetic activation with excessive surge of noradrenaline at the cardiac nerve terminals resulting in noradrenaline overflow spilling over the myocardium) [1,37–41].

Three other hypothetical pathologic mechanisms have also been mentioned in the literature. Evidence supporting these hypotheses is insufficient. Lyon et al. [42] in a report about TS suggested a pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. They believe that high levels of circulating epinephrine trigger a switch in intracellular signal trafficking in ventricular cardiomyocytes, from Gs protein to Gi protein signaling via the $ß_2$-adrenoceptor. This switch to $ß_2$-adrenoceptor-Gi protein signaling protects against the proapoptotic effects of intense activation of $ß_1$-adrenoceptors and has also a negative inotropic myocardial effect leading to ventricular wall motion abnormality. Cocco and Chu [43], in a review article, claim that hypoplastic branching of the coronary arteries in the apical region of the heart may explain the apical localization of the left ventricular wall motion abnormality in TS. Regional differences in ß-adrenergic receptor density and sympathetic innervation with increased responsiveness of the left

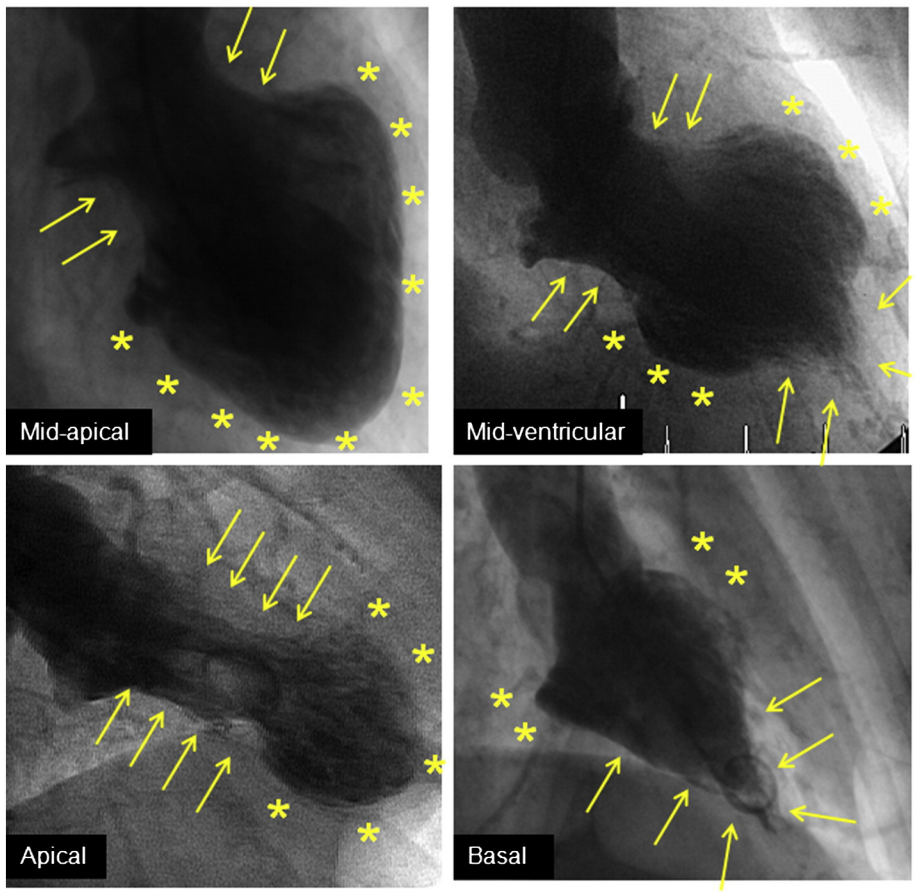

Fig. 2. Left ventriculography during systole in four cases with TS in the right anterior oblique projection shows the typical regional left ventricular ballooning.