TAKOTSUBO SYNDROME

Definition

Takotsubo (octopus pot in Japanese) syndrome also referred to as stress cardiomyopathy, is a disorder associated with left ventricular dysfunction.[1,2] Thus, it is not a typical cardiomyopathy by means of a chronic disease.[3]

Epidemiology

The true incidence of stress cardiomyopathy is unknown, but due to an increased awareness and recognition it has been rising (15-30 cases per 100,000 per year).[4] Takotsubo syndrome occurs usually in old women with a mean age of 67-70 years (50% of them with neurologic or psychiatric conditions) after emotional or physical stress, but a substantial proportion of patients are younger than 50 years of age, and the disease may be seen even in the absence of stress.[5,6] Takotsubo syndrome is estimated to represent approximately 2– 3% of all, and 5–6% of female patients presenting with suspected STEMI.[1,2] It accounts for 0.02% of hospitalizations in the United States, and recurrence rate is estimated to be 1.8% per-patient year.[1] LV ballooning may be apical (81%), midventricular (15%), basal (2%) or focal (1.5%).[5]

Aetiology

The mechanisms of disease remain unclear and the cause has not been established, but catecholamine-induced myocardial injury is the most established and well-known theory.[1,2] Chemotherapy using chimeric antigen receptor T cell and tumour-infiltrating lymphocytes is an established cause of Takotsubo syndrome in patients with cancer.[7]

Pathophysiology

Acute stressors induce brain activation, and increase bioavailability of cortisol and catecholamine. A circulating epinephrine surge leads, through multiple mechanisms, such as direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and increased cardiac workload, to myocardial damage, which has a functional counterpart of transient apical left ventricular ballooning. Stress-induced prolonged vasoconstriction may be due to adverse (broken hearts) or pleasant emotional events (happy hearts).[8] Catecholamine-induced myocardial injury, however, does not explain all the clinical features and presentations of the condition, and numerous other pathways and abnormalities are emerging.[2,3] Invasive tracing of pressure-volume relations has indicated reduced cardiac contractility, a shortened systolic period, inefficient energetics,

and prolonged active relaxation but unaltered diastolic passive stiffness. These findings may suggest decreased phosphorylation of myofilament proteins.[9]

Impaired microvascular perfusion, myocardial inflammation, and electrophysiological dearrangements also contribute to its clinical manifestations.[10] Myocardial and systemic inflammatory activation, with myocardial macrophage infiltration and acute proinflammatory monocyte and cytokine activation has been demonstrated for at least 5 months after the initial attack.[11] The relative preponderance among postmenopausal women suggests that estrogen deprivation may play a facilitating role, probably mediated by endothelial dysfunction.[12] Patients predisposed to takotsubo stress cardiomyopathy typically have a low cardiovascular risk factor profile but reactive airways disease and affective psychiatric disorders.[13] Thus, stress cardiomyopathy represents a form of neurocardiogenic myocardial stunning, and while the link between the brain and the heart is established, the exact pathophysiological mechanisms remain unclear.[4]

Diagnosis

Usually patients present with acute heart failure, although the condition may also be asymptomatic. AF and atrial flutter are not uncommon (up to 25%) and indicate adverse prognosis.[14] Cardiac arrest is relatively common and is associated with worse outcomes. Typically, it occurs at presentation, but may occur in the subsequent acute phase.[15] Diagnostic criteria and a diagnostic algorithm have been proposed (Tables 1 and 2, and Figure 1).[16,17]

The ***ECG*** typically shows signs of acute or anterior myocardial infarction. Other specific ECG changes are T-wave inversion, often deep and widespread, and substantial QT prolongation, usually developing 24 to 48 hours after the onset of symptoms or the precipitating stressful trigger. ST-segment elevation involving precordial leads is seen in ≈40% of cases. The shark-fin sign, described in high-level stressors like critical illness, is an uncommon electrocardiographic finding that typically results from the fusion of the QRS complex, ST segment, and T wave (Figure 2).[18]

Echocardiography reveals systolic and diastolic dysfunction almost indistinguishable from acute MI due to LAD occlusion.[19]

Troponin elevation (0.01-5.3 ng/ml) is the rule.[20]

Cardiac MRI and echocardiography display characteristic features. Figure 3 depicts the most common types of stress cardiomyopathy. A focal type may also rarely occur.[5] Average LVEF is 32 to 36%.[20,21] Approximately 4% have right or left ventricular thrombus.

The ***Bio-TAK score*** with biomarkers reflecting myocardial stress (NT-proBNP)), vasoconstriction and anxiety regulation (PAM: peptidylglycine α-amidating monooxygenase), atherosclerotic plaque instability (sLOX-1: soluble lectin-like oxidized

low-density lipoprotein receptor-1), LDL, and sex, may facilitate accurate early rule-in and rule-out of Takotsubo syndrome.[22]

Therapy

A general therapeutic scheme is presented in Figure 4.[16]

Beta blockers are theoretically promising but they may not offer protection.[5,20]

ACE inhibitors or ***ARBs*** are essential.[5]

Anticoagulation should be considered in the presence of ventricular thrombus while or embolic events. Standard heart failure therapy is administered when needed. Early restoration of normal ventricular function is the rule but in 5% of the patients it can be delayed (>2 months). Approximately 5% of patients have a recurrence 3 weeks to 4 years after the first event.[20]

In hospital mortality is 2-4% and during long-term follow up mortality is 5.6% per year.[5,20,21] Takotsubo is associated with severe complications requiring intensive care, particularly in younger patients.[6] Recurrence is reported to occur in 1.8% per patient-year.[5] Although previously thought to be a benign, self-limiting condition, recent studies have confirmed that patients with takotsubo syndrome have persistent subtle ongoing cardiac dysfunction, and many continue to have limiting symptoms despite restoration of left ventricular ejection fraction.[2] Thus, long-term outcome is highly variable, being more favorable when the syndrome is triggered by emotional events than when it develops in response to physical or neurologic conditions.[17] Takotsubo cardiomyopathy is associated with long-term structural and metabolic alterations in the myocardium, and patients should be counseled since they may develop long-term heart failure.[23]

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