

Hyponatremia: An Uncommon Trigger for Takotsubo Cardiomyopathy

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Abstract

Background: Takotsubo or stress cardiomyopathy is a cause of reversible left ventricular systolic dysfunction in the absence of coronary artery disease.

Methods: Cardiomyopathy is rather frequent in post-menopausal, older women. In these, the pathogenesis is induced by physical or emotional stressors in the absence of protective effect of estrogen on cardiovascular system. But, some endocrine stimuli (thyroid dysfunction surrenal insufficiency, diabetes mellitus, hypoglycemia pheochromocytoma) act as less frequent triggers of Takotsubo cardiomyopathy (TC).

Results: Hyponatremia, as expression of some pathologies ranging from nephrotic syndrome, cardiac failure and polydipsia, or as manifestation of syndrome of inappropriate secretion of antidiuretic hormone (SIADH), can also act as trigger of TC.

Conclusions: Hyposodiemia also acts by catecholamine excess deriving from the central nervous system and reduced serum levels of Na⁺, that impairs the Na⁺/Ca⁺⁺ myocardial membrane pump.

Keywords: Takotsubo Cardiomyopathy; Endocrine and dys-Autonomic Triggers; Hyponatremia; SIADH

Abbreviations

TS: Takotsubo Syndrome; LV: Left Ventricle; CVD: Cardio-Vascular Disease; SIADH: Syndrome of Inappropriate Anti-Diuretic Hormone.

Introduction

Apical ballooning syndrome, otherwise called Takotsubo Syndrome (TS), broken or stress-cardiomyopathy, is an acute, transient decrease in left ventricular function that mimics an acute myocardial infarction [1,2]. The syndrome is characterized by acute chest pain and/or dyspnea with ST-segment and T wave abnormalities at electrocardiogram (Figure 1), reversible left ventricular apical dyskinesia and elevation of troponin levels, in the absence of obstructive epicardial coronary arteries (Figure 2) [3]. Cardiomyopathy is diagnosed in 1-2% of patients initially presenting with symptoms suggestive of acute coronary syndrome but, unlike that, it is often completely reversible [2].

Several variants of TS were described. Typical echocardiographic finding consists of a hyperkinetic LV base with apical akinesis resulting in apical LV ballooning (Figure 3). Other variants are: LV basal hypokinesis and apical hypercontractility, midventricular hypokinesis and both basal and/or apical hypercontractility [4].

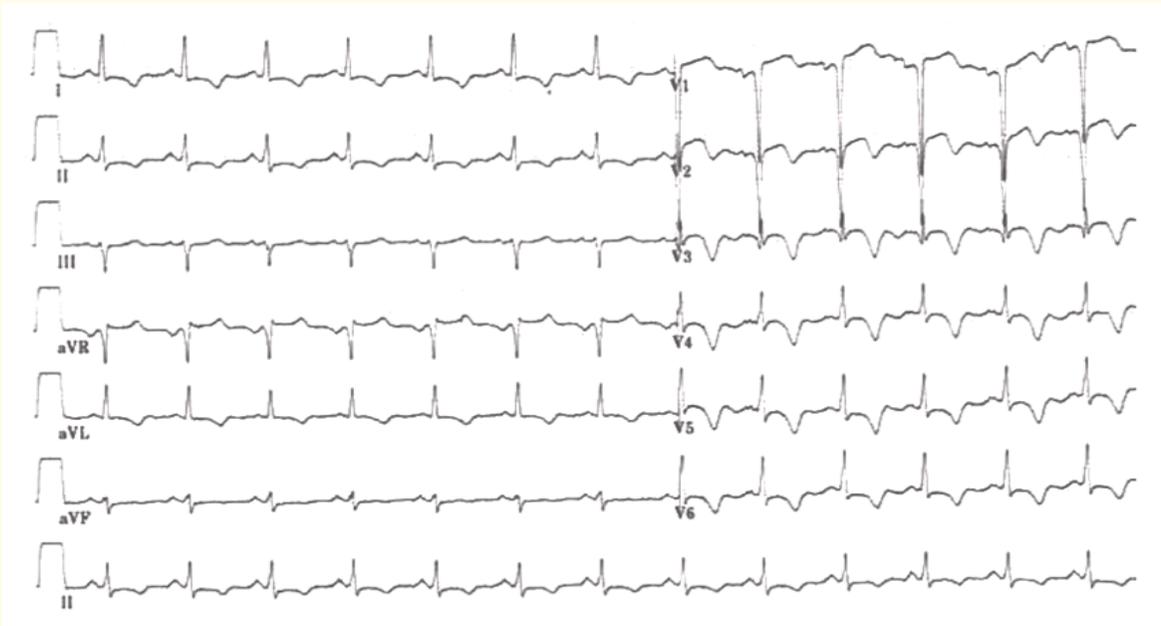


Figure 1: 12 leads-e.c.g. in Takotsubo cardiomyopathy-T waves inversion in antero-lateral derivations.

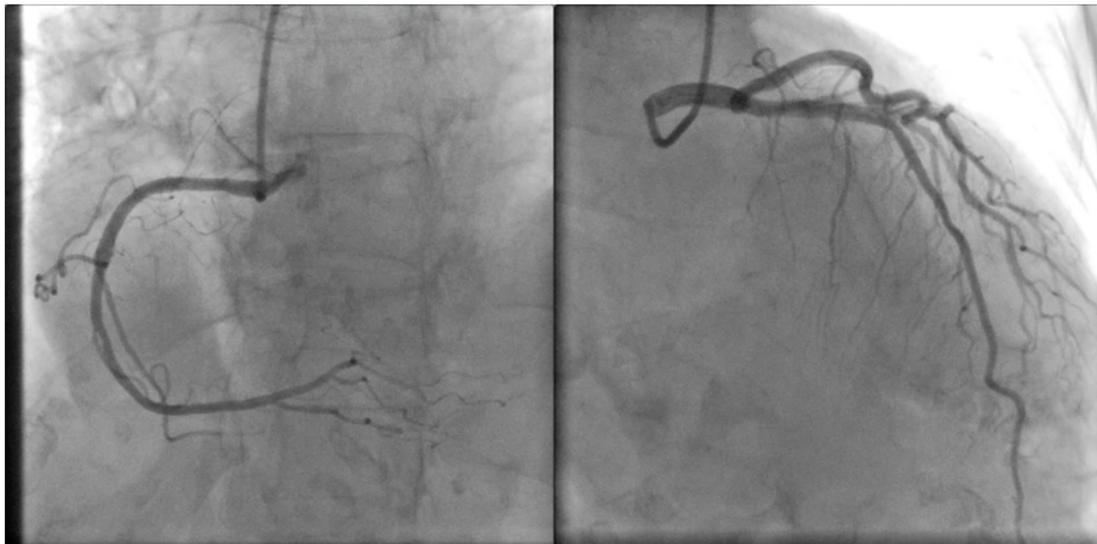


Figure 2: Left and right coronary angiogram demonstrating normal epicardial coronary arteries.

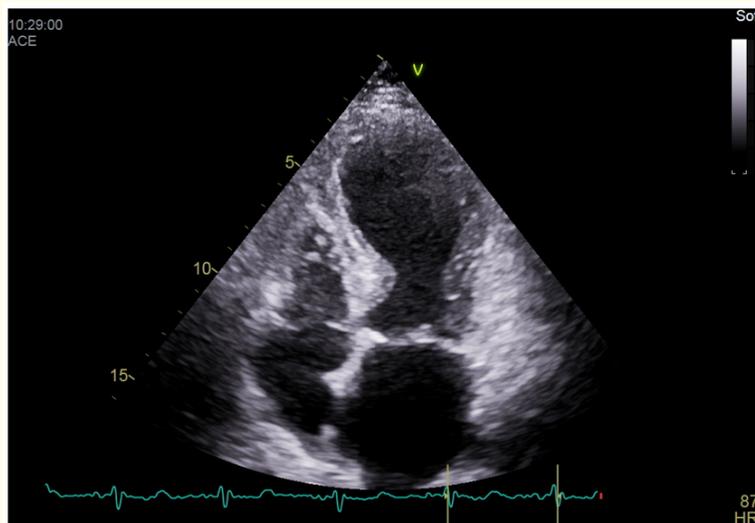


Figure 3: Transthoracic echocardiography-4-chamber view showing left ventricular dysfunction with apical hypokinesis.

Pathogenesis

The precise mechanism responsible of TS is unknown, even if catecholamine toxicity plays a fundamental role. Catecholamines' excess is related to the stress acting as initial trigger [5]. There are emotional, physical, medical, surgical, neurological, or psychiatric stressors, that favour catecholamines' excess. On the other hand, catecholamines may induce shifting of β -adrenergic receptors from stimulatory G protein at the apical myocardium, causing a reduction of contractility (myocardium stunning) [6]. In addition, catecholamines are responsible for direct cardiotoxicity, coronary microcirculatory dysfunction, multifocal coronary spasms, hyperviscosity and hypoperfusion, that contribute to the signs and symptoms of cardiomyopathy [7].

These conditions mainly concern the myocardium of post-menopausal women. Concerning this, epidemiologic studies have suggested that pre-menopausal females have a reduced incidence of cardiovascular disease (CVD) when compared to age-induced males. But, its incidence and severity increased in post-menopause, because the protective effect of estrogen on cardiovascular system is lacking. In turn, lack of estrogen in the postmenopausal state may predispose women to the actions of catecholamines' excess [8,9].

Other predisponent conditions

Apart this mechanism concerning the aetiology of TS regarding postmenopausal women, that are the leading receivers of the syndrome, other numerous conditions can trigger TS in all subjects. In these are included:

1. Thyroid dysfunction (hyper-or-hypothyroidism) is a condition favouring catecholamines' excess that, acting as trigger of TS [10,11]. Particularly, thyroid hormones favour the catecholamines' action on the left ventricle, inducing apical stunning. Nevertheless, it is still unclear whether the pathogenesis of TS in these patients with is related to thyroid functional state solely or it is a confounding factors [12,13].
2. Several lines of evidence suggest that an exaggerated adrenergic response, in combination with suppressed parasympathetic modulation of the heart (dys-autonomia), at emotional or physical stimuli may induce TS. Concerning that, Kaufmann et al. reported an unusually high norepinephrine levels in patients with TS occurred after emotional or physical stress. On the contrary, their index of parasympathetic modulation was significantly decreased. These combined data still confirm that an impaired baroreflex control may play a role [14].

3. Independently of catecholamines release, adrenal insufficiency caused by an insufficient glucocorticoid production [15], can cause TS. In fact, glucocorticoid plays an important role in myocardial contractility, in maintaining myocardial inotropy and calcium transport across cardiac sarcoplasmic reticulum [15-17]. Thus, its deficiency favours myocardial stunning.
4. Diabetes mellitus, often associated with autonomic neuropathy, when a stressor is present may exert a potential influence on TS pathogenesis [18].
5. Psychological stress induced by acute hypoglycemia (anorexia nervosa) may act as a potential trigger for stress cardiomyopathy [19,20].
6. Pheochromocytoma is a neuroendocrine tumor arising from chromaffin cells in the adrenal medulla. Paroxysmal hypertension, headaches, diaphoresis and palpitations were the symptoms of catecholamines' excess deriving from pheochromocytoma. It may trigger the autonomic (sympathetic) nervous system and results in sympathetic cardiac nerve terminal disruption and norepinephrine spillover. This causes left ventricular wall motion abnormality located at apical or mid-ventricular region [21].

Hyponatremia

An uncommon trigger able to induce an increase of catecholamines in central nervous system, is hyponatremia. That occurs in several conditions as: volume overload (cardiac failure), nephrotic syndrome, cirrhosis, endocrinopathies, and polydipsia.

Clinical manifestations of hyponatremia (usually limited to central nervous system) are evident when the concentration of Na⁺ in the plasma is abnormally low (<115 mg/dL at least) [22].

Physical findings of hyponatremia include the following

- Confusion, disorientation, delirium.
- Muscle weakness, tremor, hypokinesia.
- Ataxia, dysarthria, Cheine-Stokes respiration, coma.

Mechanisms inducing TS

Likewise previous conditions, high catecholamine levels, secondary to Na⁺ deficiency, may directly injure myocytes or indirectly cause multivessel epicardial or microvascular coronary spasm [2]. In addition, the impaired function of the myocyte membrane sodium-calcium pump induces intracellular calcium overload, responsible for myocardial dysfunction [23].

A peculiar form of hyponatremia, constituent one-third of all cases and dependent on specific causes is the syndrome of inappropriate antidiuretic hormone (SIADH). It is due to the action of ADH or Vasopressin, that acts by reducing the diuresis with water retention, concomitant hypo-osmolality and high urine osmolality in the absence of renal, adrenal and thyroid insufficiency. The syndrome is the result of an excess of water rather than a deficiency of sodium [24-26].

The Na⁺ depletion in SIADH depends on several conditions as [27]:

- Medicines, such as certain drugs of type 2 diabetes, antidepressants (venlafaxine), cancer drugs, some drugs reducing blood pressure;
- Stroke, infections and brain disorders;
- Lung diseases (cancer, infections, tuberculosis, pneumonia);
- Hypothalamus or pituitary diseases;
- Cancer of the lung (small-cell);
- Mental disorders.

Diagnostic criteria of SIADH are defined by Bartter and Schwartz [28]:

- Hyponatremia with hyperosmolality;
- Renal retention of sodium;
- Urine less than maximally dilute;
- Absence of other causes of hyponatremia;
- Correction of hyponatremia by fluid restriction.

Therapeutic measures include some measures such as fluid restriction, hypertonic saline and loop diuretics. [29,30]. Recently, vasopressin receptor antagonist, called as Tolvaptan, has been introduced as specific therapy of SIADH. The drug appears advantageous to patients because it no need for fluid restriction and the correction of hyponatremia can be achieved within a short time [30].

Conclusive Remarks

TS is a reversible cardiomyopathy, that typically occurs in post-menopausal women. Catecholamines' excess seems to exert a main action as consequence of activation of some triggers, even the precise mechanism is still unknown. Apart this modality (more evident in older females), some endocrine and autonomic abnormalities can cause reversible cardiomyopathy with identical mechanism.

Severe hyponatremia, a very common electrolytes' disorder, represents an unusual condition that rarely may induce TS, as referred in some case reports [31,32]. In hyponatremia, the reversible dysfunction of apical left ventricle seems to be dependent by the stimulation of nervous central system, responsible for catecholamines increase. In turn, catecholamine excess may trigger myocardial injuries. But, the reduced Na^+ levels may act on $\text{Na}^+/\text{Ca}^{2+}$ membrane pump, interfering with myocardial inotropism associated with hypotonicity.

However, other studies performed in a wide range are requested to better evaluate the detailed modalities by hyponatremia can induce TS.

Authors Contribution

Fulvio Cacciapuoti and Federico Cacciapuoti contributed equally to the work. Pio Caso contributed to the supervision and references.

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