TAKOTSUBO CARDIOMYOPATHY (LEFT VENTRICULAR BALLOONING SYNDROME) INDUCED DURING DOBUTAMINE STRESS ECHOCARDIOGRAPHY.

N.Elazaoui[1], H.Lardoux[2], R.Habbal[1]
[1]Cardiology department, CHU Ibn Rochd, Casablanca, Morocco.
[2]Function tests "Explorations fonctionnelles" Unit, IHFB, Paris, France.

Corresponding author:
Dr Noura El Azaoui, MD
Adress: Cardiology department, CHU Ibn Rochd, Casablanca, Morocco.
Tel.: 00212667366415
E-mail: elazaoui.nora@gmail.com

Abstract:

Takotsubo cardiomyopathy is increasingly recognised as a syndrome, usually provoked by severe mental stress and associated with acute "ballooning" or dyskinesis of the left ventricle. Although the etiology of takotsubo syndrome remains obscure, catecholamines release appears to be the principal trigger. The case presented in this article illustrates how the use of catecholamines stressors in an already anxious patient induced an acute Takotsubo syndrome mimicking acute myocardial infarction. It is likely that other cases of Dobutamine stress echocardiography (DSE) induced myocardial infarction is in fact due to takotsubo syndrome.

Keywords: Apical ballooning syndrome echocardiography, Takotsubo cardiomyopathy, stress cardiomyopathy, strain.

Introduction:

Stress cardiomyopathy Takotsubo is a recent clinical entity that mimics acute coronary syndrome [1] and is defined by a reversible myocardial stunning secondary to stress [2]. Initially described in the 1990's [3], the first cases of Japanese Takotsubo were published in 2001, paving the way for numerous publications. The prevalence of Takotsubo syndrome is estimated between 1.7% and 2.2% of patients admitted to hospital for suspected acute coronary syndrome [3].It occurs mainly in women, and usually after a physical or emotional acute stress [5]. During stress echocardiography, few cases of Takotsubo have been reported, and the exact mechanism is poorly understood. We report a patient who experienced an acute episode of Takotsubo induced by DSE [5].

Case report

60 years old woman with risk factors (diabetes and high blood pressure), treated with Metformin and Aprovel was referred to our Stress Echo unit for a DSE, because of several episodes of chest pain. In the past, she presented a depressive syndrome, a gastro-esophageal reflux, and a normal coronary angiogram in 2009, because of atypical chest pain. DSE was performed using a standard protocol with progressive increment of Dobutamine (10 to 30 gammas) and 0.50 followed by 0.25 mg Atropine IV. At peak stress (maximum heart rate = 154/min; 99% FMT), DSE was considered as positive with chest pain, and nausea, EKG abnormalities in infero apical leads (fig1). Premature ventricular beats, septo-apical akinesia and infero-basal hypokinesia were observed during recovery, and abnormal global longitudinal strain was obvious during late recovery (basal-21.8%, recovery -13.8%) (Fig1). Because of the persistence of the symptoms, the patient was admitted in CCU: normal physical exam, no hemodynamic instability, sinus rhythm and antero-septal ischemia on EKG and troponin was abnormal, 2.5ng /ml.

Cardiac magnetic resonance imaging (MRI) confirms the existence of Takotsubo syndrome with left ventricular medial and moderate LV dysfunction with an ejection fraction measured at 50%. Echocardiography found unexpanded left

ventricle with severe hypokinesia of the apical wall of the middle septum, middle sidewall, middle lower wall and the anterior wall means LVEF 35%. Coronary angiography found angiographically normal coronary Takotsubo with ventricular mid syndrome ventriculography (Fig.2).

Evolution, LVEF complete recovery, ECG and troponin normalization to 3 weeks later.

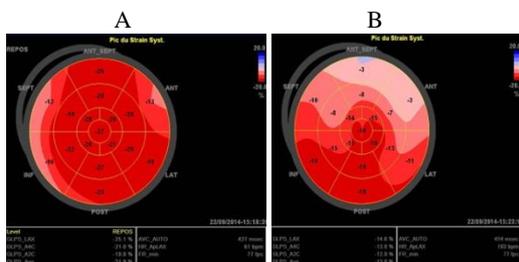Fig 1: atypical ST elevation in V3/4 and in inferior territory

A   B

Fig.2: Strain longitudinal global

 A: Normal segmentation score Basal: SLG -21.8%
 B: Alteration of the segmentation score recuperation: SLG -13.8%
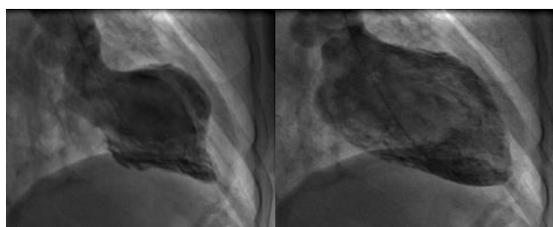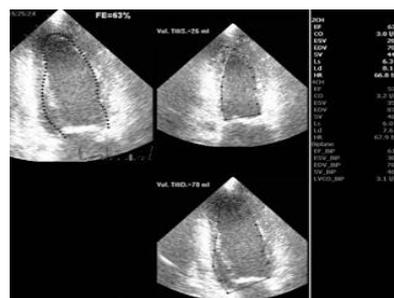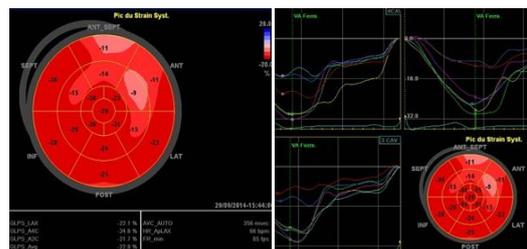

Fig.3: Coronary ventriculography

Fig. 4 : SLG à -21.5% et FEVG à 63%

Discussion

In Japan, Takotsubo is a terracotta pot for capturing octopus ("tako" means an octopus, and "tsubo" pot). This name was given to an array of acute cardiomyopathy, usually triggered by a stressful situation and characterized by reversible abnormalities in contractility of the left ventricular apex creating a transitional ballooning of the left ventricular apex, evoking the form a "Takotsubo".
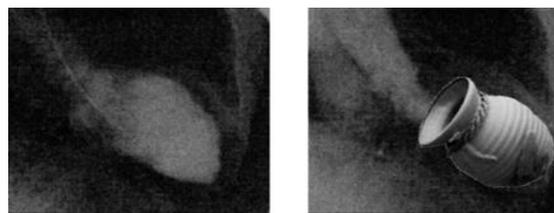

図 8　症例3の入院時（左）と１週間後（右）の左心室造影像
典型的な「ツボ型」左心室造影である。
Sato et al. Kagakuhyouronsya, 1990

Patients typically present chest pain symptoms, electrocardiographic modifications (elevation or ST-segment depression, Q wave) and enzyme elevation with angiographically normal coronary arteries [1]. In their study princeps, Tsuchihashi and al. report that 18 patients presented in triggering acute stress or annoyance, in other cases it was systemic disorders, surgical pathology or peranesthesic period [1]. A few cases have been reported demonstrating the potential for ESD transient apical ballooning to induce a syndrome (TAKOTSUBO) (**Table 1**), although the exact mechanism is poorly understood.

Table I: Reported case of Takotsubo [14,15]

Reported cases of takotsubo cardiomyopathy following DOB stress.

Author	Year	Age	Gender	Peak DOB	Atropine	Phase
Silberbauer	2008	75	Female	30	0.5 mg	Peak
Cherian	2008	85	Female	40	No	Peak
Margey	2009	61	Female	40	No	Peak
Mosley	2010	50	Female	30	0.5 mg	Peak
		74	Female	40	0.25 mg	Peak
Shah	2011	85	Female	30	No	Recovery
Ho	2012	83	Female	40	0.5 mg	Recovery

DOB, dobutamine (mcg/kg/min).

Electrocardiographic tracings show that the changes affecting preferentially leads V3 and V4 and the ST-segment elevation and Q wave are transient signs that fade in sub-acute period (only 10% of patients still have a Q wave J 21 ± 11). All patients had initial apical ballooning with a mean ejection fraction measured at 41 ± 11% increasing significantly to 64 ± 10% three weeks later, but our patient recovery time was one week (**Fig. 4**).

Pathophysiological assumptions

The triggering circumstances (stress Externally or internally) suggest that the causative mechanism is related to sympathetic over activity, particularly catecholaminergic origin (by analogy with acute cardiomyopathy pheochromocytoma) whose consequences can be a direct myocardial toxicity and / or microvascular vasoconstriction associated with some degree of endothelial dysfunction (**Fig. 5)**
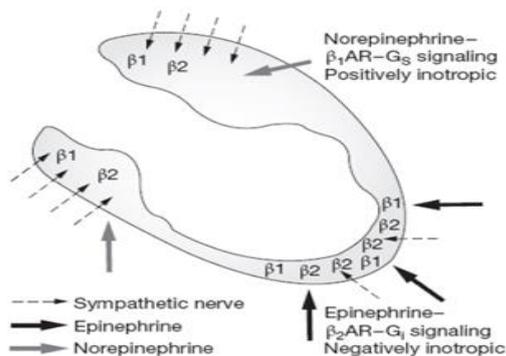

Fig.5: catecholergic mechanism [25]

Stress and catecholamines liberation

Medulla seems to be the key effector of the sympathetic response to physiological stress (mainly adrenaline production with significant

involvement of adrenergic receptors in the heart catecholergic). The adrenergic receptors, mainly a1 type, are present at the surface of cardiomyocytes. Their activation increases intracellular calcium influx by modifying permeability of the cytoplasmic membrane with, if significant, catecholaminergic discharge excess including intracellular calcium creating a direct myofibrillar toxicity, cell necrosis [6]. The free radicals and intracellular excess oxidized metabolites of catecholamines also participate in the lesional process.

Experimentally, a model of Takotsubo has been described in rats when the forced immobilization stress exposure leads to an LV in 50% of cases, generalized hypokinesia of the left ventricle, and in 50% of cases apical ballooning [6] a phenomenon inhibited by combined blockade of receptors a and b. In rabbits, increasing doses of noradrenaline creates myocyte damage limited only to the use of phentolamine (a-blocker), alone or in combination with a beta-blocker, but not with single b-blocker.

An autopsy series of 15 patients who died of assault shows no myocyte injury in 13 of them [7]. These data are found in the clinic, where the tests of circulating norepinephrine and epinephrine were high for the majority of patients with an array of Takotsubo [1]. Similarly, Pavin et al. relate adrenaline and noradrenaline levels as high as than four times the standard eight hours after admission in a patient with normalization in three days. [4]. Mechanisms could be explained in our patient with dobutamine echocardiography.

Various forms of left ventricular dysfunction are reported in stress cardiomyopathy, such as apical ballooning and mid ventricular dysfunction, but the underlying causes have not been fully elucidated. Myocardial stunning, where brief periods of ischemia owing to vasospasm lead to transient structural, metabolic and functional abnormalities, has been suggested as a cause of symptoms. [8]

Vasospasm of coronary arteries

Noradrenaline, the neurotransmitter of efferent sympathetic fibers, can trigger vasoconstriction in vascular smooth muscle cells (VSMCs) through stimulation of α-adrenergic receptors. Clinical studies have confirmed that Coronary Artery Spasm (CAS) can be induced by catecholamines[9]or by stimuli (eg, exercise, cold pressor test)[10,16] that increase sympathetic outflow. In addition, the induction of CAS by some substances (eg, cocaine, amphetamines) has been suggested to be related to sympathetic activation and/or VSMC sensitization to catecholamines.[17] Furthermore, it is known that β-blockers may exacerbate angina attacks in

patients with variant angina, probably because of the blockade of vasodilator coronary β2 receptors, which leaves vasoconstrictor α-adrenergic receptors unopposed.[18] However, it has been found that an increase in coronary levels of catecholamines may follow, rather than precede, spontaneous ischemic episodes of CAS.[19] Moreover, α-blockade has often been shown to be ineffective in controlling symptoms in variant angina patients.

In physiological conditions, acetylcholine, the neurotransmitter of parasympathetic nerve fibers, causes vasodilation through the endothelial release of NO, whereas at high doses it may induce vasoconstriction through direct stimulation of VSMC muscarinic receptors. Thus, in case of VSMC hyperreactivity, even small concentrations of acetylcholine might induce CAS. In the clinical setting, some findings suggest a role for vagal activity as a trigger of spasm. In patients with variant angina, attacks often occur during the night, when vagal tone is higher,[20 ,21] and the intracoronary administration of acetylcholine is known to induce CAS.[22]

However, the relationship between acetylcholine-induced CAS and the role of vagal activation in triggering spontaneous spasm in patients remains uncertain. Indeed, the frequent occurrence of ischemic episodes during the night does not necessarily imply that CAS is induced by vagal activation. The assessment of cardiac autonomic changes associated with spontaneous episodes of ST-segment elevation has indeed shown that ischemic episodes are often preceded by a reduction, rather than by an incrementation of vagal activity. [23]In agreement with these data, the occurrence of vasospastic angina attacks at night is more frequent during the rapid eye movement phases of sleep, when vagal withdrawal occurs in association with an increase in adrenergic activity.[24] . [11]Some investigators have used provocative tests, such as infusion of ergometrine or acetylcholine to evaluate the frequency of inducible coronary vasospasm in stress cardiomyopathy, with inconclusive results. A review of the existing literature showed that multivessel vasospasm could be induced in 24 (28.6%) of 84 patients with stress cardiomyopathy (95% CI 20–39%). This finding was confirmed by another literature review that showed positive provocative test results in 27.6% of 28 patients with stress cardiomyopathy [12]. It is, therefore, difficult to determine whether myocardial stunning as a result of epicardial coronary artery vasospasm is an underlying or main cause of stress cardiomyopathy.

Obstruction of the Left Ventricular Outflow Obstruction (LVOT)

Some patients, especially elderly women, may be predisposed to developing a dynamic LVOT obstruction, perhaps due to the presence of a sigmoid-shaped interventricular septum, a smaller LVOT, reduced LV volumes, or an excessively mobile mitral valve apparatus.[13] The LVOT obstruction in these patients may become manifest upon intense adrenergic stimulation.

We believe that our patient experienced stress-induced cardiomyopathy with a dynamic LVOT obstruction that was precipitated by the dobutamine. The emotional anxiety associated with the test, the chemical stress of the dobutamine, or both, could have caused the cardiomyopathy. In addition, the dobutamine might have aggravated the hyperkinetic basal segments of the patient's LV, thereby worsening the LVOT obstruction and further stressing the myocardium.

Because the incidence of LVOT obstruction in stress cardiomyopathy is low, it remains uncertain whether these changes are a consequence than a cause of stress cardiomyopathy.

Conclusion

Dobutamine echocardiography is a diagnostic test used widely, and few, however, induce Takotsubo syndrome under catecholergic effect and transient or dynamic obstruction of the left ventricular outflow chamber.

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