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Review

Practical update of Takotsubo syndrome☆

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ABSTRACT

Takotsubo syndrome, apical ballooning or "broken heart" syndrome, is a growing diagnostic entity which clinically mimics an acute coronary syndrome. Included into the stress cardiomyopathy group of cardiopathies, this condition is characterized by the absence of potentially responsible coronary lesions, while displaying a transient abnormal ventricular motion, usually affecting various coronary territories. It is generally observed in postmenopausal women and frequently seen in the presence of a stressful situation, both physical and emotional. With a prevalence of 1.2% among patients undergoing a cardiac catheterization with a suspected diagnosis of acute coronary syndromes, Takotsubo syndrome usually has a good prognosis. However, complications can occur in the acute phase, generally heart failure, which can even lead to death. In this review we discuss the latest available information on this disease and present it in a practical and useful way for the attending physician.

Actualización práctica en síndrome de Takotsubo

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RESUMEN

El síndrome de Takotsubo, *apical balloning* o síndrome del «corazón roto», es una entidad de diagnóstico creciente que mimetiza clínicamente un síndrome coronario agudo. Englobado en el grupo de las miocardiopatías de estrés, se caracteriza por la ausencia de lesiones coronarias potencialmente responsables del cuadro y una paradójica alteración en la motilidad ventricular de carácter transitorio, que suele interesar varios territorios coronarios. Se observa generalmente en mujeres posmenopáusicas y se describe con frecuencia la presencia de una situación estresante, tanto física como emocional. Con una incidencia aproximada del 1,2% de aquellos síndromes coronarios agudos sometidos a cateterismo, a pesar de conllevar generalmente un buen pronóstico, ocasionalmente presenta en la fase aguda complicaciones, generalmente insuficiencia cardiaca, que pueden conducir incluso al fallecimiento de los enfermos. En la presente revisión nos planteamos repasar la última información disponible y presentarla de un modo práctico y útil al clínico.

Takotsubo syndrome is a disorder described by Sato and Dote in the late 80s in Japan, which usually manifests, both clinically and biochemically, as an acute coronary syndrome.[1–3] Interestingly, it is worth noting the fact that the imaging tests usually show a left ventricle motility impairment which includes various coronary regions without causal obstructive lesions being observed in the coronary angiography (Table 1).[3–7] In addition, segmental abnormalities are fully recovered (stunning) in a few days and in a good number of cases patients report a recent stressful situation, so it was described as stress cardiomyopathy or broken heart syndrome.[4,6–12] Other names, such as transient apical dyskinesia, "ampulla" syndrome or even the name Takotsubo syndrome itself is derived from the curious systole-like shape which the left ventricle adopts in the acute phase ("takotsubo" meaning octopus trap pot in Japanese).[4,7,8]

Originally described in Japanese, cases were then reported in all continents, races and ages.[1,2,4,12–14]

In the next few lines we will try to detail, as concisely as possible, the current situation regarding knowledge of this curious

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Table 1
Takotsubo syndrome diagnostic criteria used in the RETAKO National Registry (based on those modified by Mayo Clinic, 2008).

1	Transient abnormalities in left ventricular contractility (dyskinesia/akinesia or hypokinesia), with or without apical involvement; extending beyond a particular coronary artery; occasionally triggered by a stressful situation, but not always
2	Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3	New electrocardiographic changes (ST elevation and/or T-wave inversion) and slight troponin elevation
4	Absence of myocarditis

disease, which is based almost exclusively on, more or less, extensive series of patients with that disease and a limited number of basic studies.

Classification

Initially, depending on the ventriculography image (Fig. 1) or other imaging tests, as per degree of acute myocardial involvement, we will differentiate the following types of Takotsubo syndrome[4,7,15,16]:

1) Typical forms *(apical ballooning)*. The most common, over 2 thirds of the cases, affects the apical region and midventricular segments, which either, do not move – systolic thickening – or are dyskinetic, with compensatory basal hyperkinesis.
2) Atypical forms or variants, without apex involvement. A variety of types have been reported, such as involvement of midventricular segments,[16] isolated lateral or lower side, only the basal portions (inverted forms),[15] associated or isolated right ventricle involvement, etc.

Lately, some authors have proposed, including ourselves, a work classification with prognostic implications,[3,14,17] as follows:

- Primary forms. Those that happen without an obvious cause -idiopathic- and, perhaps, those occurring after the patient suffers extreme psychological stress (e.g. death of a relative, robbery, mugging).
- Secondary forms. Those occurring in a severe concomitant illness setting, which possibly determines a worse long-term prognosis (e.g., after an asthma attack, major surgery, a lung embolism, thyrotoxic crisis, etc.). They account for around 20% of cases.[14,17,18]

Epidemiology

As its incidence is difficult to estimate accurately because it is a rare and possibly underdiagnosed condition, it gives the impression that it has increased in recent years. This may be due, among other factors, to an increased knowledge of doctors about the disease linked to a generally more invasive management of acute coronary syndromes, often with early coronary angiography, even in elderly patients.[4,10,12,19–21] Japanese series have reported an acute coronary syndrome incidence of 1.2–2.2%; 2.2% in the USA; 0.3–2.3% in Germany; and in Spain, the national registry on the disease (RETAKO), shows a 1.2% of catheterizations indicated with acute coronary syndrome diagnosis, having analyzed 202 consecutive patients between 2012 and 2013.[22] Table 1 shows the diagnostic criteria used in the previously mentioned record. Some studies, which were only evaluating postmenopausal women reported up to 5.9%, with a prevalence of atypical forms.

The profile of the patient, usually consistent in most published series,[20–22] includes a female prevalence (about 90%), common cardiovascular risk factors, generally hypertension in more than half of the cases, and diabetes or smoking in a slightly lower number. In the RETAKO registry, 50% of patients referred a significant psychological stress situation, 20% physical stress (surgery or trauma), 3% reported both and about 27% could not find any trigger.[22] Although a clear seasonal or daily distribution was not found in the Spanish multicenter study, some authors have described a summer prevalence, while others a winter one.[22] What seems clear is that, as other cardiovascular disorders, significantly stressful global situations, such as earthquakes or football world championships, may be associated with Takotsubo "outbreaks".[22,23]

Clinical signs and symptoms

By far, the most common symptom is chest pain (33–100%, 80% in RETAKO), which may manifest atypical characteristics or angina-like symptoms, making it indistinguishable from this condition. Vegetative symptoms are often associated. However, cases have been reported whose symptom index was dyspnoea, syncope or even cardiac arrest. The latter, without chest pain, are usually associated with the secondary forms.[21,22]

When its clinical presentation is that of an acute coronary syndrome, it is often accompanied by different grades of heart failure, sometimes even worse than in acute coronary syndromes without ST-segment elevation (fig. 2), making the careful management of these patients advisable.[7,20,24]

Diagnosis

Although many diagnostic criteria have been proposed, initially by Japanese groups, and later by many other groups, in a disease that is diagnosed by exclusion of other diseases, we usually recommend the criteria modified by the Mayo Clinic (Table 1). For diagnosis, it is essential to verify the normalization of ventricular segmental abnormalities (except in cases of exitus).[3,4,6–8]

Diagnostic tests

Next, the most important findings in each diagnostic level will be briefly detailed.[22,24]

- *Lab test results:* an elevation of myocardial necrosis biomarkers is observed, usually troponin, due to being more sensitive, which is within the range of acute coronary syndrome but in contrast with a significantly higher degree of ventricular dysfunction, as reflected by imaging tests. Other markers such as BNP or derivatives have been shown usually high, with uncertain prognosis meaning. D-dimers, occasionally elevated, or thyroid profile, usually normal, do not generally establish the diagnosis but can be very useful in uncertain cases. The PLATAKO study, which compared a small number of cases of Takotsubo syndrome with acute coronary syndromes (matched by elevation or non-elevation of ST), did not find a causal role for platelets, as in atherothrombotic infarctions (type I).[25] In contrast, it is worth noting that it agrees with the paradigmatic study by Wittstein et al., which showed higher blood concentrations of circulating catecholamines in patients with Takotsubo than in patients who had a heart attack, despite involving a degree of heart failure.[26] In the PLATAKO study, after the acute phase, a trend ($p = 0.06$) showing higher levels of circulating catecholamines was observed in patients who had suffered from Takotsubo when compared to those who had a heart attack.[25,26]