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EDITORIAL COMMENT

Takotsubo syndrome: We are still ''halfway''. A complex heart-brain duality?

Síndrome de Takotsubo: ainda estamos a «meio do caminho» . . . *Uma complexa dualidade coração-cérebro?*

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Takotsubo syndrome (TTS) was first described in the early 1990s in the Japanese population. It was named takotsubo because of the resemblance of the shape of the left ventricle (LV) in systole to a Japanese octopus trap called a takotsubo.[1]

Although more than 30 years have passed, it is still not fully understood. There are different hypotheses for the underlying mechanism, one of the most commonly accepted being the theory of catecholamine-induced cardiotoxicity in response to an emotional or physical stimulus.[2]

This syndrome has previously been associated with a benign course, but more recent data have shown that a significant rate of in-hospital complications may be seen, and that the short- and medium-term prognosis may be less favorable than previously thought.[3,4]

Data from studies in Portugal, including registries, have certainly contributed to a better understanding of this condition.[3,5] The initial results published from the International Takotsubo (InterTAK) Registry showed that more than half of the patients with TTS (55.8%) had a history or an acute episode of a neurologic or psychiatric disorder, conditions that were evident in only 25.7% of patients with an acute coronary syndrome.

The spectrum of TTS was wide, with low to very high risk in the acute phase. The physical triggers and acute neurologic or psychiatric diseases were among the factors associated with an increased incidence of acute complications. Also, patients had substantial rates of death and complications after the acute phase. Regarding medical therapy, the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), but not of beta-blockers, was associated with improved survival at one year.[3]

Another observational, retrospective study, that evaluated the use of beta-blockers in the acute phase, found neither a beneficial nor harmful association between early beta-blocker use and in-hospital mortality.[6]

In this edition of the Portuguese Journal of Cardiology, Raposeiras-Roubín et al.[7] present an interesting study which aims to assess the impact of beta-blocker therapy (patients that have received beta-blockers at discharge) in long-term mortality and TTS recurrence. The cohort used was from the national Spanish Registry on TTS (RETAKO Registry). It is a partially retrospective and prospective (since 2012)

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observational study from 38 centers in Spain. Considering the exclusion criteria, 970 (from 1095) patients were included and divided into groups according to the types of preceding stressors (emotional stress, physical stress and no identifiable trigger); the pattern of LV dysfunction was classified in apical and non-apical type. The considered follow-up outcomes, after hospital discharge, were defined as the first non-fatal TTS recurrence or the occurrence of all-cause of death (mean follow-up of 2.5±3.3 years). The main results were:

(a) 60% of the patients were treated with beta-blockers;
(b) there were 87 deaths (3.6 per 100 patients/year) and 29 TTS recurrences (1.2 per 100 patients/year);
(c) even after multivariate adjustment, no significant differences in the composite outcome of mortality or TTS recurrence between patients treated and untreated with beta-blockers were found (the same result in a propensity score analysis);
(d) no benefit of beta-blockers in follow-up mortality and/or TTS recurrence, across all TTS types;
(e) regarding the trigger, beta-blocker therapy was most frequently prescribed in the TTS group related to emotional stress, but no significant differences in the follow-up outcomes were found;
(f) in a subgroup analysis (considering age, gender, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease (COPD), Killip class, cardiogenic shock, ACE inhibitors/ARB at discharge) no benefit of beta-blockers was found in any subgroup, with an increase in mortality and recurrence rates of TTS in COPD.

The results presented by Raposeiras-Roubín et al.[7] are in line with other earlier studies.[3,6]

The several study limitations are addressed by the authors and consist of, among others, the heterogeneity of beta-blocker therapy (dose and type), and rates of discontinuation or new prescriptions during follow-up. These data were not collected and might have affected the outcomes.[7]

There are very few studies that have evaluated the impact of the type of beta-blocker on clinical outcomes in TTS, but beta-blockers that activate β2 adrenoceptor (to inhibitory G protein signaling) may be deleterious, as they might exacerbate the epinephrine-induced negative inotropic effect.[8]

Although there have been no randomized trials to define the optimal management in this syndrome, beta-blockers are one of the most frequently prescribed therapies at discharge.[9]

Regarding this problematic, studies like the one presented by Raposeiras-Roubín et al.[7] also alert the clinician to the need for more investigation and trials, for a better understanding of the pathophysiology and therapeutic management of TTS, in order to use a more appropriate approach, with possible implications for its course.

TTS is heterogeneous, not only with different clinical profiles, triggers, and anatomical shapes but also with different recovery times. Another study from InterTAK Registry addresses this issue. In-hospital outcomes and one-year mortality were compared for patients with versus without early recovery of LV wall motion abnormalities (the cut off for early recovery was defined as 10 days after the acute event). The authors found that 53% of the patients presented late LV improvement. The absence of an early recovery showed unfavorable one-year outcomes compared with an early recovery. Male sex, lower LV ejection fraction and acute neurologic disorders were among the factors associated with the absence of an early recovery.[4]

Besides the issue of the therapeutic approach, maybe we should ask a broader question: how can we improve the management of such a complex entity? We certainly still have some way to go. One of the gaps is in the knowledge of the pathogenic mechanisms.

A recent position paper on pathophysiology of TTS mentioned that all the complex mechanisms and changes that can happen within the heart need to be integrated at a systems biology level, with peripheral vasculature, the brain, and autonomic and peripheral nervous system. Given this, the recognition of key pathways in the heart, vasculature and brain could be future targets for new treatments, with possible diagnostic and therapeutic impact in TTS, in the acute phase and subsequently. A correct and earlier diagnosis may also be of relevance to the better management of this syndrome.[10]

More data from prospective studies, randomized and controlled trials are warranted to better identify the mechanisms underlying this syndrome, its treatment and follow-up.

It is of special interest whether medical treatment influences the outcome, especially after the acute phase. This will also require a better understanding of this complex heart–brain duality in order to clarify the pathophysiology and, consequently, the therapy and prevention in this syndrome.

Takotsubo syndrome is as complex and challenging as it is fascinating.

Conflicts of interest

The author has no conflicts of interest to declare.

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