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REVIEW

Takotsubo syndrome in Heart Failure and World Congress on Acute Heart Failure 2019: highlights from the experts

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Abstract

Takotsubo syndrome was featured in various sessions and posters at the recent Heart Failure Congress and World Congress on Acute Heart Failure 2019 held in Athens. The importance and increasing recognition of this acute heart failure syndrome is reflected by the growing activity at Heart Failure Association congresses over the last 8 years. Two dedicated sessions to Takotsubo syndrome with comprehensive lectures from experts in the field and several posters highlighted new scientific progress, important aspects of epidemiology, pathophysiology, risk stratification, and management of the syndrome and discussed gaps in knowledge of this intriguing entity. This paper will summarize the topics discussed in these sessions including the most recent data from large registries, clinical, and pre-clinical studies presented at the meeting.

Keywords arrhythmias; heart failure; takotsubo syndrome; transplantation

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Introduction

Heart Failure 2019 Congress, the largest congress worldwide about heart failure (HF) with more than 5400 attendees this year in Athens, covered almost every modern topic in HF, justifying the title: *Heart failure from Alpha to Omega*. Takotsubo syndrome (TTS), a relatively recently described clinical entity, included in the differential diagnosis of the causes of acute HF, is an important medical condition discussed at the congress. The growing understanding of its pathophysiology, the numerous challenges in its treatment but also its research interest, made TTS sessions (Table S1) popular for attendees. A range of new information and expert opinions were presented at the meeting, which we summarize in this article.

Epidemiology

Data from the nationwide Swedish Coronary Angiography and Angioplasty registry confirm the preponderance of women in TTS population with a percentage of 73%.[1] Men with TTS have disproportionally worse prognosis than women. From the same registry, it is obvious that TTS differs between different health care regions within Sweden with the highest reported incidence in the Western health care

region, whereas mortality is higher in the Southern region.[2] The temporal pattern of TTS is similar to that of acute coronary syndromes (ACS) with peak during winter, while the least cases of TTS appear in spring and of ACS in summer.[3]

Definition

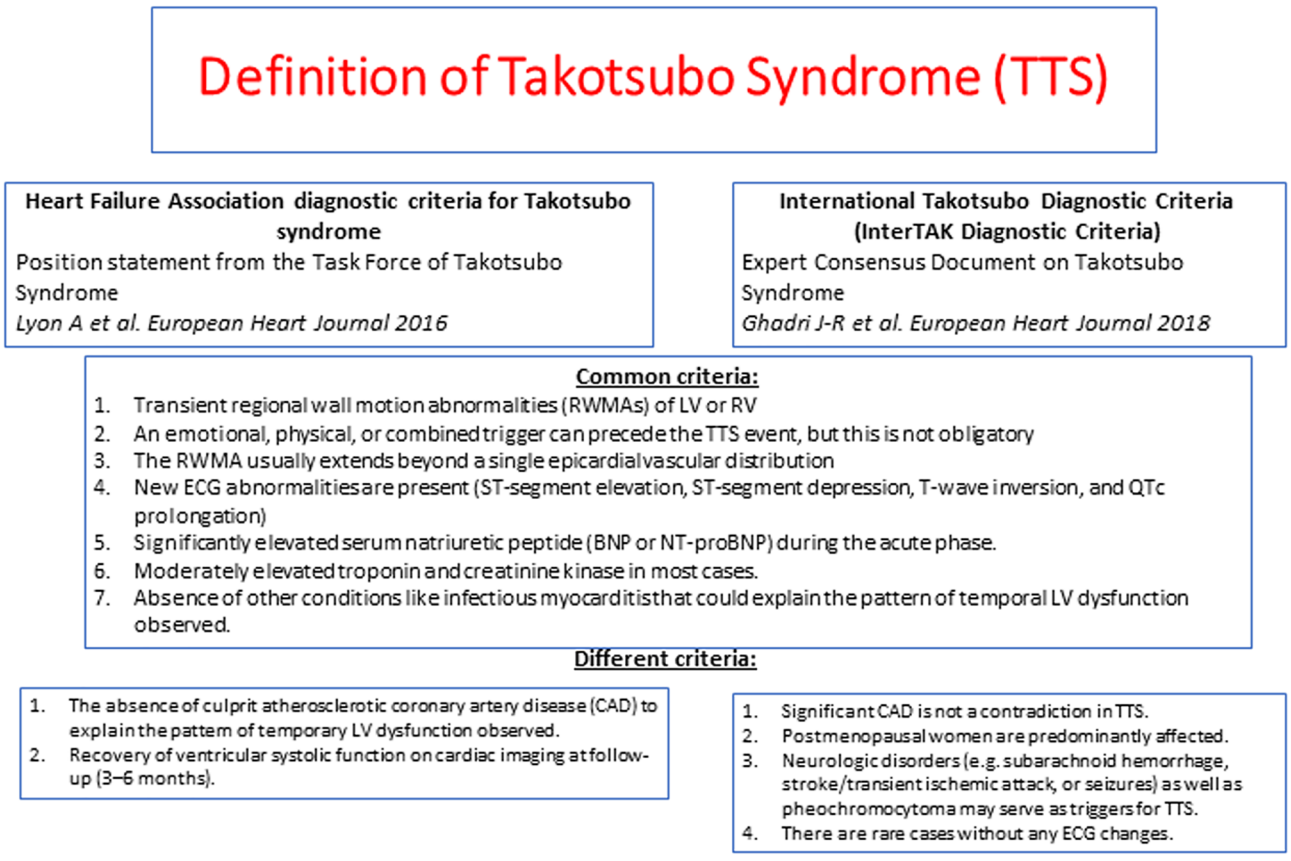
The definition of TTS according to the two most recent position papers[4,5] involves several diagnostic criteria (*Figure 1*), most of which are common and include transient regional wall motion abnormalities (RWMAs) of the left ventricle (LV) and/or the right ventricle (RV) after a stressful trigger (emotional, physical, or combined, neurologic disorders, or pheochromocytoma), RWMAs extend beyond the distribution of a single coronary artery, new and reversible electrocardiographic (ECG) abnormalities, elevated serum natriuretic peptides, and relatively small troponin elevation.

The InterTAK diagnostic score[6] includes seven criteria (female sex, physical trigger, emotional trigger, absence of ST depression, psychiatric disorder, neurologic disorders, and QTc prolongation). A score $>$ 70 increases significantly the possibility of TTS, but as Dr Di Vece underlined, the predicted probability of TTS depends on the prevalence of the disease in the population applied and in clinical practice, coronary imaging is essential to exclude other diagnoses. LV end-diastolic pressure may be normal, near normal, or elevated in TTS whereas it is usually elevated in ACS.[7]

Although transient myocardial dysfunction is considered a prerequisite in the definition of TTS, there is evidence that myocardial recovery is not full 4 months after the acute phase of TTS, demonstrated by deformation indices[8] and also cardiac energetic status and intense myocardial oedema.[9] Professor Dana Dawson presented the results of HEROIC study[10] and even a year after the acute episode, there is persistent subclinical cardiac dysfunction. Unremitting symptoms compatible with HF, cardiac limitation on exercise testing, significantly impaired deformation mechanics, and cardiac energetic status reaffirm the long-term structural, functional, and metabolic changes in TTS patients.

Professor Omerovic and Dr Di Vece presented two cases that proved that TTS and coronary artery disease can co-exist. Approximately 15% of patients with TTS have concomitant coronary artery disease with significant impact upon outcomes. Another issue is that in one third of patients, there

Figure 1 Similarities and differences between Heart Failure Association and International Takotsubo Diagnostic Criteria.



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is no trigger—physical or emotional according to International Takotsubo Registry.[11]

RWMAs define the type of TTS with apical TTS (typical type) being the most common (~80%). Atypical types of TTS (midventricular, reversed, and focal) have distinct patterns in echocardiographic images or in ventriculography. Diagnosis of focal TTS can be challenging. Apical TTS presents with the lowest LV ejection fraction (LVEF) in the acute phase, while after 60 days, there is no significant difference in LV systolic function between the different types. There is some controversy in the literature concerning long-term prognosis. Ghadri *et al*.[12] reported that all TTS types have similar prognosis after 1-year follow-up from the large InterTak registry, while another study suggests that apical TTS is associated with higher mortality within the first 6 months but after complete recovery of LV systolic function, prognosis is the same.[13] Dr Di Vece reported that patients with TTS enrolled in an Italian registry with LVEF $\leq$ 35% at presentation are at higher risk not only in the acute phase but also at long-term follow-up.[14]

Diagnosis

ECG changes comprising of ST segment elevation, T wave inversion, QT prolongation and less frequently left bundle branch block, atrial fibrillation, and ST depression are typical of TTS, but a normal ECG does not exclude the diagnosis.[11] Dr Yoshihiru Akashi reviewed the ECG changes observed in TTS patients. Dr Akashi explained that ST depression in aVR and absence of ST elevation in V1 suggest TTS with sensitivity and specificity $>$ 90%.[15] Troponin elevation is usually disproportionally low to the extent of myocardium involved, while NT-proBNP levels are higher at admission compared with ACS.[16] Echocardiography[17] and cardiac magnetic resonance[18] are the main imaging modalities used in the diagnosis of TTS, and its complications provide significant prognostic information. A comprehensive diagnostic algorithm in the emergency department can be used to differentiate TTS vs. ACS or myocarditis.[19]

Pathophysiological insights

Several clinical and preclinical studies support the central role of sympathetic nervous system and catecholamines in TTS by inducing myocardial stunning. Dr Ciccarelli described how catecholamine levels are markedly higher in patients with TTS compared with matched controls and patients with left anterior descending artery occlusion and ST elevation myocardial infarction.[20] Nonetheless, the central role of catecholamines in TTS is demonstrated by intravenous study administration of catecholamines, and beta-receptor agonists led immediately to the development of TTS.[21] Another interesting observation from preclinical studies is that norepinephrine predominately is released in basal myocardial regions where sympathetic innervation is highest, while epinephrine has the greatest effect in apical regions where β-adrenoceptor density is highest. Norepinephrine is the main catecholamine released from sympathetic nerve endings, whereas epinephrine among circulating catecholamines. These heterogeneities may explain the RWMAs in TTS because of changes in adrenoceptor density and/or sensitivity, as well as alterations in downstream signalling pathways.[22]

G protein-coupled receptor kinases (GRKs) are tightly related to the adrenergic system through mechanisms of desensitization and down-regulation, and they also seem to play a role in the pathophysiology of TTS. Specifically, L41Q polymorphism of GRK5, one of the two isoforms predominant in the heart, makes patients susceptible to TTS.[23,24] An interesting study showed that GRK2 and β-arrestin 2 expression in the myocardium was higher in TTS than in dilated cardiomyopathy or controls in the acute phase, supporting the concept that β-adrenergic receptors on the cell membrane are modified by GRK2 and β-arrestin 2, confirming their role in the development of LV dysfunction in TTS.[25]

Risk assessment—prognosis

Professor Elmir Omerovic highlighted that TTS is not a benign condition as it is associated with significant complications such as acute HF, mitral regurgitation (MR), cardiogenic shock, and malignant ventricular arrhythmias that can impact on prognosis.[4] RV involvement is present in 15% of TTS patients with increased in-hospital rate of major adverse cardiovascular events.[26] Risk stratification of patients with TTS should take into account numerous variables including age, systolic blood pressure, presence of pulmonary oedema, MR, apical thrombus, new ventricular septal defect or LV rupture and LVEF and LV outflow track obstruction (LVOTO).[4] TTS has substantial morbidity and mortality, with rate of major adverse cardiovascular events 9.9% per patient-year and rate of death 5.6% per patient-year in the International Takotsubo Registry with long-term follow-up.[11]

Arrhythmias

In the risk stratification of patients with TTS, certain arrhythmias/ECG characteristics should be taken in account; ventricular tachycardia, ventricular fibrillation, QTc $>$500 ms, abnormal Q wave, and prolonged ST elevation are considered factors of high-risk patients.[4] QTc prolongation is also included in the diagnostic criteria of InterTAK Diagnostic Score, adding six points to the total score.[5] QRS duration on admission has significant prognostic impact, with prolonged duration associated with higher incidence of all-cause death,

cardiac death, ventricular arrhythmias, atrioventricular block, use of catecholamines, and various circulatory support devices.[27] Recently Jesel *et al*.[28] showed that 105 ms is the optimal cut-off value of QRS duration for predicting the risk of life-threatening arrhythmias. The presence of J wave is another factor that is associated with increased risk of cardiac death and cardiac arrhythmia in TTS patients.[29] Negative prognostic risk factors are also high heart rate on admission and atrial arrhythmias, including atrial fibrillation and atrial flutter.

Dr Olivier Morel delivered his lecture focusing on the arrhythmias seen in TTS patients and the underlying cardiac electrophysiology. The prevalence of atrial arrhythmias in TTS is 18–25%, and they are associated with higher in-hospital mortality, 30-day mortality, all-cause mortality, and cardiovascular mortality.[30] Supraventricular arrhythmias could be related to atrial stretch/impairment, but inflammation has possibly a role too.[31]

The prevalence of ventricular arrhythmias is 2–10%, and the prevalence of all life-threatening arrhythmias including torsades de pointes, ventricular fibrillation, complete heart block, sinoatrial block, asystole, and pulseless electrical activity is 13.5%.[28] Most ventricular arrhythmias occur within the first 24 h and are associated with significantly worse short-term and long-term prognosis. Catecholamine surge, inflammation/oedema, ischaemia, and lack of estrogens are the main pathophysiological mechanisms responsible for electrical instability in TTS. Therapeutically, implantable cardioverter defibrillator implantation is not indicated as the arrhythmic risk is generally transient, while there is an indication for pacemaker implantation, if atrioventricular conduction abnormalities persist.

Management

Dr Alexander Lyon reviewed the clinical management of TTS and emphasized that currently there have been no trials to guide management decisions and therefore current pathways of care are based on expert opinion and depend upon the type of TTS (primary or secondary) and the level of risk. In case of secondary TTS where there is also another medical or surgical emergency, it is important to optimize treatment of the underlying condition to lower sympathetic drive.

Lower risk patients with LVEF $>$ 45% do not need any treatment, while if LVEF is 35–45%, an angiotensin-converting enzyme inhibitor and a beta-blocker are recommended in the recent Heart Failure Association (HFA) position statement.[4] Dr Lyon explained that in his opinion, carvedilol is the preferred choice if there is no LVOTO, while β_1 adrenergic receptor specific blockers are preferred in cases of severe LVOTO.[4] Higher risk patients with TTS should be treated in coronary care unit or high dependency units setting for at least 72 h. Additionally, if there is an apical thrombus, low-molecular-weight heparin should be administered and then oral anticoagulation for at least 3 months. The role of direct oral anticoagulants vs. warfarin needs to be defined.

In the advanced cases of cardiogenic shock, extracorporeal membrane oxygenation or left ventricular assist device should be considered, but if not available, then levosimendan can be used, starting at low dose and up-titrating slowly. Avoidance of nebulized β2 agonists, iatrogenic catecholamines, and QTc prolonging drugs and stopping selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors are also important.

Dr Lyon argued that long-term follow-up and care are needed in cases with ongoing cardiac symptoms and recurrent TTS. Chronic chest pain, exertional dyspnoea, and arrhythmias are the main chronic symptoms. In his experience, carvedilol, ranolazine, and diltiazem may be helpful, while non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors should be avoided. Electrophysiology review and ablation of refractory atrial and ventricular arrhythmias are the suggested treatments if symptomatic and refractory to medical therapy in patients with TTS.

Psychological support and stress management counselling are considered to play key roles in the chronic treatment of TTS patients, and support groups on Facebook or patient support websites (www.takotsubo.net) provide patient-centred support. Special reference must be made to spontaneous and recurrent TTS cases where it is recommended to screen these patients for pheochromocytoma.

Case reports

Interesting cases were presented as posters or moderated posters illuminating the co-existence of TTS with other clinical entities, such as Guillain–Barre syndrome,[32] pathology of the coronary arteries (spontaneous dissection),[33] or as a phenocopy of apical hypertrophic cardiomyopathy (HCM).[34] Typical TTS in the acute phase can mimic apical HCM because of ECG changes and apical RWMAs, making the diagnosis of HCM or TTS possible only after recovery. Another instructive case presented by Zaw et *al*.[35] demonstrated a possible association of HCM with TTS, suggesting that the responsible pathophysiologic mechanism could be basal septal hypertrophy and catecholamine driven LVOTO. Treatment of TTS in patients with severe MR and LVOTO, if complicated with acute pulmonary oedema, should be cautious with regards to diuretics and nitrates, as they can increase LVOT gradient.[36]

A unique case of cardiotoxicity was presented by Belarte Tornero *et al*.[37] with TTS evolving to cardiogenic shock in a patient with BRAF-mutated metastatic lung cancer under treatment with trametinib.[37] Suppression of MEK and ERK1/2 activation in the heart is the suggested underlying

mechanism, and periodic cardiac screening may be necessary in patients treated with trametinib.

A case of successful cardiac transplantation from a donor with TTS was presented by Professor Omerovic E. The donor was a 59-year-old woman with subarachnoid haemorrhage, mid-ventricular akinesia, and LVEF ~35% who met the ESC Takotsubo working group criteria for secondary TTS. The recipient was a middle-aged man with biventricular congestive HF because of dilated cardiomyopathy. Cardiac function of the transplanted heart recovered within 2 weeks. This case belongs to a cohort of donors with TTS (n = 42) from the same group. New onset of left ventricular dysfunction in organ donors is frequent and considered as a contraindication for utilization of the heart. However, such dysfunction is often caused by TTS and is therefore transient. The Gothenburg group has recently shown (38) that transplantation of hearts from donors with TTS has similar long-term survival as from donors with normal heart function. If proven true by randomized clinical trial, this strategy could lead to increase organ availability by ~25% and therefore improved survival and quality of life in patients with terminal HF.

Gaps in knowledge

There are several issues concerning pathophysiology, treatment, and prognosis that require further research to improve our understanding of the syndrome and patients' outcome. What is the cause of akinesia with the characteristic pattern in LV and/or RV? Why do some individuals develop TTS while others with the same triggers do not? Is there a genetic or environmental substrate? Why there is such a preponderance of postmenopausal women? What is the endocrine–cardiac specific interaction in women that makes them susceptible to this syndrome? How do patients with TTS and extensive LV dysfunction survive while patients with myocardial infarctions of comparable extent of affected myocardium do not? What are the responsible mechanisms for LV recovery? What are the predisposing risk factors for life-threatening arrhythmias? Is inflammation a causative factor or an effect of TTS? What is the best treatment strategy in this population in the acute phase but also long term? What should be the duration of medical treatment of patients with TTS in case of complete and/or incomplete LV recovery?

Conclusions

Interesting research and expert opinion regarding the management of TTS was presented in HFA 2019 Congress. Many more questions were also discussed, highlighting the need for additional research and clinical trials. The next HFA Congress will be hosted in Barcelona in May 2020 and will review the clinical management of TTS, new insights into pathophysiology, and hopefully provide the answers to many of the questions raised at the recent 2019 HFA Summer Congress.

Conflict of interest

For Linda W. Van Laake: The UMCU, which employs Dr. Van Laake has received speaker, advisory board or consultancy fees and/or research grants from Abbott, Vifor, Novartis, Medtronic, Roche and Sopachem. Alexander R. Lyon reports receiving speaker, advisory board or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Amgen, Clinigen Group, Takeda, Roche, Eli Lily, Eisai, Bristol Myers Squibb, Ferring Pharmaceuticals and Boehringer Ingelheim

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Takotsubo syndrome sessions during 'Heart Failure and World Congress on Acute Heart Failure 2019'.

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