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EDITORIAL

Cardiac arrest and Takotsubo syndrome

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This editorial refers to 'Cardiac arrest in Takotsubo syndrome', by S. Gili *et al.*, doi:10.1093/eurheartj/ehz170.

Takotsubo syndrome (TTS) is a condition characterized by acute heart failure and transient ventricular contractile dysfunction that is frequently precipitated by acute emotional or physical stress. A wide variety of emotional and physical stressors have been associated with this syndrome and, while acute stress is temporally related to syndrome onset in the majority of patients, up to a third of patients in some series have no identifiable antecedent trigger at the time of presentation.[1] The syndrome typically affects older post-menopausal women, though men account for ~10% of reported cases.[2] The incidence of TTS is higher than initially thought, and accounts for up to 5–10% of women presenting with a suspected acute coronary syndrome. Patients with TTS typically present with chest pain, dynamic electrocardiographic (ECG) changes, and elevated cardiac biomarkers, but characteristic features of the syndrome that help to distinguish it from an acute myocardial infarction include the absence of plaque rupture and coronary thrombosis, unique patterns of ventricular dysfunction that typically involve more than one vascular territory (the 'ballooning' patterns), and rapid and complete recovery of ventricular systolic function. There has been increased awareness and recognition of this syndrome by clinicians worldwide over the past several years, but the precise pathophysiology of TTS remains poorly understood. Numerous pathogenic mechanisms have been proposed, but the preponderance of evidence suggests that the contractile dysfunction characteristic of TTS is probably catecholamine mediated.[3] Enhanced adrenergic stimulation following emotional or physical stress may induce transient myocardial contractile dysfunction through a variety of mechanisms that include ischaemia due to sympathetically mediated microvascular dysfunction and direct cardiotoxicity from catecholamine-mediated myocyte calcium overload.[3]

While TTS was initially felt to be a fairly benign condition, larger series have demonstrated significant morbidity and mortality with this syndrome.[1] The prognosis of patients with TTS appears to be at least in part dependent on the inciting trigger. Patients with emotional triggers have a generally favourable prognosis, while patients with TTS secondary to neurological injury and other physical triggers have higher mortality rates than patients presenting with acute coronary syndromes.[4] TTS has been associated with a wide variety of serious complications including life-threatening arrhythmias (LTAs) and cardiac arrest. Reported LTAs have included atrioventricular block, asystole, polymorphic and monomorphic ventricular tachycardia, and ventricular fibrillation.[5] The mechanisms of ventricular arrhythmogenesis are likely to be variable and may include sympathetically mediated early afterdepolarizations, catecholamine-mediated QT interval prolongation with pause-dependent torsade de pointe or ventricular fibrillation, and electrical instability due to myocardial oedema.[5] The incidence of LTAs in TTS has been reported in various series to be 2–10%, but most of these series have been small and have not sufficiently explored the natural history of cardiac arrest in TTS.[6,7] Therefore, the true incidence of cardiac arrest in TTS and its impact on both short- and long-term outcomes remain unknown.

In this issue of the *European Heart Journal*, Gili and colleagues take a major step forward in elucidating the frequency, clinical features, and prognostic importance of cardiac arrest in patients with TTS.[8] The authors reviewed the records of 2098 patients from The International Takotsubo Registry (InterTAK Registry) and identified 124 patients with cardiac arrest. Twenty-one of these patients lacked heart rhythm data during the arrest and were excluded from analysis. Therefore, the clinical features and outcomes of 103 patients with cardiac arrest and an established heart rhythm during the event were compared with 1928 TTS patients without cardiac arrest. Of the 103 patients with cardiac arrest, the authors were careful to distinguish those patients initially presenting with cardiac arrest (n = 84) from those who developed cardiac arrest during the acute phase of TTS (n = 19). The main outcomes were 60-day and 5-year mortality, and independent predictors of mortality and cardiac arrest during the acute phase were also investigated.

Several important observations were made in this study. The frequency of cardiac arrest in this cohort of patients with TTS was 5.9%. While this is consistent with previous reports,[1,9] the current series is by far the largest reported to date and reinforces that life-threatening arrhythmias and cardiac arrest are not uncommon in TTS. The occurrence of cardiac arrest in TTS, whether at the time of presentation or during the acute phase of the syndrome, identified a very high-risk group of patients with an in-hospital mortality of 35% and a six-fold increase in 60-day and 5-year mortality compared with TTS patients

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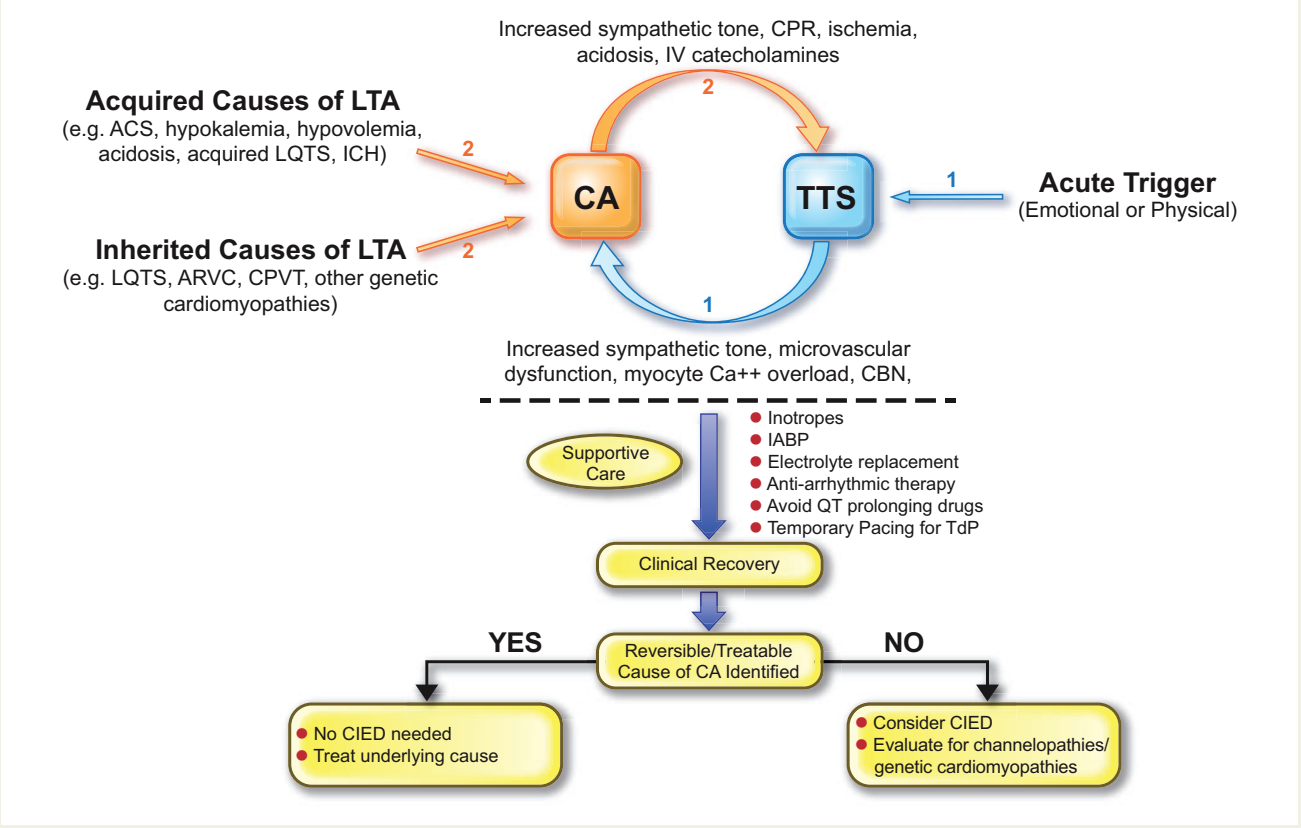

Figure 1 Approach to the patient with Takotsubo syndrome (TTS) presenting with cardiac arrest. TTS can be either the cause or the consequence of cardiac arrest. Patients may develop TTS from an acute emotional or physical trigger and may then present with cardiac arrest as the initial manifestation of the syndrome (scenario 1). Alternatively, individuals who suffer a cardiac arrest from either acquired or inherited causes of life-threatening arrhythmias can develop TTS due to the excessive sympathetic stimulation of the arrest itself and the intravenous catecholamines that accompany the resuscitation (scenario 2). In either scenario, the initial focus should be on haemodynamic support and arrhythmia management while treating the underlying acute illness. In patients where an acute trigger and/or reversible cause for the cardiac arrest cannot be identified, an implantable device for secondary prevention and/or rhythm management should be considered. ACS, acute coronary syndrome; ARVC, arrhythmogenic right ventricular cardiomyopathy; Ca^{++}, calcium; CA, cardiac arrest; CBN, contraction band necrosis; CIED, cardiac implantable electronic device; CPR, cardiopulmonary resuscitation; CPVT, catecholaminergic polymorphic ventricular tachycardia; IABP, intra-aortic balloon pump; ICH, intracranial haemorrhage; IV, intravenous; LQTS, long QT syndrome; LTA, life threatening arrhythmia; TdP, torsades de pointes.

without cardiac arrest. This increase in short- and long-term mortality occurred despite recovery of left ventricular function and therefore may have reflected adverse non-cardiac sequelae from the initial trigger or more significant co-morbidities in this population. Predictors of mortality following cardiac arrest included male sex, T-wave inversion on ECG, and intracranial haemorrhage. The reason for lower mortality in women is unknown, but may be related to a partially protective effect of oestrogen on endothelial and microvascular function during periods of hyperadrenergic stimulation.

The current study highlights that the majority of cardiac arrests observed in TTS occur at the time of presentation. Of the 103 patients with cardiac arrest, 84 (81.6%) had cardiac arrest at the time of initial presentation while only 19 (18.4%) experienced cardiac arrest in the acute phase after the diagnosis of TTS had been established. Patients presenting with cardiac arrest were more likely to have ventricular tachycardia/fibrillation, possibly reflecting a greater arrhythmic substrate in this population, while patients with cardiac arrest in the acute phase had a higher frequency of pulseless electrical activity (PEA) and asystole. This latter finding is novel since cardiac arrest in the acute phase was previously thought to be secondary to QT interval prolongation and polymorphic ventricular tachycardia.[5,10] There were otherwise no major differences between the two groups with respect to patient demographics, haemodynamics, cardiac function, or in-hospital complications and mortality. Risk factors associated with a higher frequency of cardiac arrest in the acute phase of the syndrome included male sex, atrial fibrillation, ST-segment elevation, and elevated C-reactive protein (CRP) at the time of admission. Atrial arrhythmias, ECG abnormalities, and elevated CRP can all be manifestations of increased myocardial inflammation, which has been well described in the acute phase of TTS[11] and may render these patients more pro-arrhythmic.

The findings by Gili and colleagues should aid physicians in their management of patients with TTS. Patients admitted to the hospital with the diagnosis of TTS should be monitored closely during the acute phase of the syndrome. Given the median time to cardiac arrest of 1 day [interquartile range (IQR) 0–3 days] that was observed

in this study, patients should be monitored closely for 72 h, particularly those identified as high-risk individuals (male sex, atrial fibrillation, ST-segment elevation, elevated CRP). Patients with TTS who suffer cardiac arrest, particularly men and/or those with neurological injury, should be regarded as extremely high-risk individuals who will frequently require aggressive haemodynamic and respiratory support and who have a high risk of in-hospital mortality. If these patients survive the hospitalization, vigilant follow-up will be required after discharge given the significant short- and long-term mortality demonstrated by this study.

An important and as of yet unanswered question is whether implantable cardiac devices such as pacemakers and defibrillators are indicated in patients with TTS who survive cardiac arrest. The data examining the benefit of devices in TTS are extremely limited,[9] and the current study did not examine whether the small number of patients discharged with devices received therapy or whether patients discharged without devices died from arrhythmic events. The current study demonstrates that most patients with cardiac arrest in the acute phase have PEA or asystole, probably secondary to the variety of medical, surgical, and neurological illnesses that precipitate TTS in the first place. Most of these patients will not require permanent devices once the underlying illness is treated and the QT interval has normalized. The decision of whether to place a device becomes more complex, however, when cardiac arrest is the initial presentation and TTS is subsequently diagnosed following the resuscitation. In these cases, it is simply not possible to know with certainty whether cardiac arrest is the initial manifestation of TTS or whether TTS results from the administration of high-dose i.v. catecholamines and the physical stress of cardiopulmonary resuscitation (*Figure 1*). This author is aware of several cases of TTS following cardiac arrest where no clear aetiology for the arrest could be identified. These patients were discharged without a device once there was clinical and echocardiographic improvement, only to be readmitted days or weeks later with recurrent life-threatening arrhythmias. These cases are stark reminders that TTS following a cardiac arrest may in some cases be an epiphenomenon. The presence of ventricular ballooning in these patients should not preclude a thorough investigation into possible causes of the cardiac arrest such as channelopathies and inherited cardiomyopathies, and placement of cardiac devices for secondary prevention should be considered if no treatable aetiology for the arrest can be identified (*Figure 1*). The current study by Gili and colleagues demonstrates clearly that cardiac arrest in TTS occurs frequently and portends a poor prognosis. Further studies are necessary to determine if secondary prevention strategies will be effective in improving outcomes in this uniquely challenging population.

Conflict of interest: None declared.

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