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Is Takotsubo Syndrome Still a Benign Disease? Complications (and Gender) Make the Difference

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Takotsubo syndrome (TTS) is a poorly recognized acute syndrome characterized by transient left ventricular systolic dysfunction in the absence of significant coronary artery disease, occurring mostly in postmenopausal women.[1] The mean age range of patients with TTS is between 67 and 70 years (around 80% of cases are aged >50 years), and it represents approximately 1% to 3% of all and 5% to 6% of female patients presenting with suspected ST-elevation myocardial infarction (STEMI).[2] Most patients with TTS have experienced recent psychological and physical stress, but some may be more susceptible to hormonal, genetic, psychiatric and neurological, emotional, and physical factors.[2] Moreover, even positive emotional stressors may trigger TTS.[3]

Patients affected by TTS may have comorbidities that can significantly influence the clinical course. Comorbidities may include the physical stress factors triggering TTS, whereas traditional cardiovascular risk factors (ie, arterial hypertension, dyslipidemia, and smoking) do not seem to play other than a marginal role in the setting of TTS.[4,5]

Growing knowledge is accumulating on the relationship between TTS and a series of pathologic conditions, such as coronary artery, neurologic, psychiatric, renal, and infectious diseases.[5-8]

In this issue of *Angiology*, El-Battrawy et al[9] evaluated in-hospital, and long-term incidence of thromboembolic events of 138 consecutive patients with TTS, compared with 138 sex- and age-matched patients with acute coronary syndrome (ACS) in a single center in Germany. The incidence of thromboembolic events in TTS was ≥2-fold higher than for ACS (21% vs 9%; $P < .01$) over a mean follow-up of 5 years.[9]

Although TTS has been generally considered as a benign disease since left ventricular function returns to normal within a short time, contemporary observations have modified this assumption.[10] A recent meta-regression study including 54 studies (>4600 patients) reported a death during admission of 1.8%, and a 3.5% annual all-cause mortality.[11] In fact, rates of cardiogenic shock and death of TTS patients are comparable with patients with ACS.[12] Others[13] reported that 12.6% of patients with TTS were diagnosed without coronary angiography; the lack of coronary angiography was independently associated with higher in-hospital mortality (3.0% vs 0.9%; $P < .001$). This finding may be related to misdiagnosis or undertreatment.[13]

The availability of larger samples of patients allowed more attention to gender-specific differences in outcomes of TTS where the great majority of patients are women. A study conducted on data from the National Inpatient Sample showed an in-hospital mortality rate for TTS of 4.2%.[14] However, male patients had a higher mortality rate than females (8.4% vs 3.6%, $P < .0001$), as well as a higher incidence of underlying critical illnesses (36.6% vs 26.8%, $P < .0001$).[14] In a study conducted on Medicare fee-for-service beneficiaries, in-hospital, 30-day, and 1-year mortality was 1.3%, 2.5%, and 6.9%, respectively, for principal diagnosis of TTS (primary presentation of TTS) and 3%, 4.7%, and 11.4% for secondary diagnosis of TTS (where an acute illness was the primary cause for admission).[15] Presumably in the latter group, the additional pathology influenced outcome. Worse outcomes were also observed for patients ≥85 years of age and male.[15] Data from a Spanish multicenter registry of patients with TTS confirmed a worse prognosis in men, characterized by higher in-hospital mortality (4.4% vs 0.2%; $P < .01$), longer intensive care stay (4.2 ± 3.7 days vs 3.2 ± 3.2 days; $P = .03$), and higher frequency of severe heart failure (33.3% vs 20.3%; $P = .02$).[16] Moreover, even when comparing cohorts of patients with TTS and STEMI, matched for age and gender, the long-term mortality was significantly higher in the TTS group (24.7% vs 15.1%, hazard ratio [HR] = 1.58; $P = .02$).[16] In multivariable regression analysis, male sex, as well high Killip class on admission, and diabetes mellitus were identified as independent predictors of mortality in patients with TTS.[17]

The type of stressor, emotional or physical, may play a role in differences between males and females. Physical stress was more frequent in men (30% vs 57%, $P = .005$), whereas more

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women experienced emotional or no stress.[18] In males, physical stress as a trigger event and shock or cardiac arrest as presenting symptoms were more frequent.[18] Patients with physical triggered TTS were more likely to have a malignancy, lower blood pressure, lower hemoglobin, higher serum creatinine, and higher norepinephrine levels than patients with non-physical triggered TTS. After adjusting for age, gender, trigger, malignancy, and hemoglobin level, being male (HR = 11.9, $P = .002$) and having a physical trigger (HR = 14.7, $P = .03$) were associated with in-hospital mortality.[19]

In light of recent evidence, we should reconsider the prognosis of TTS. Prognosis should be evaluated case by case, depending on the presence of concomitant factors. For example, for thromboembolic events as reported by El-Battrawy et al.[9] Also, males seem to have a higher mortality risk.

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