Gender-Related Differences in Takotsubo Cardiomyopathy

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KEYWORDS

• Takotsubo cardiomyopathy • Gender-related difference • Emotional stress • Physical stress • Cardiogenic shock • Resuscitation • Electrocardiogram • Apical ballooning syndrome

KEY POINTS

- In all studies reported so far, there is a marked gender preference in takotsubo cardiomyopathy (TTC), in which 90% of those affected are women, with a mean age of 62 to 76 years.
- Between 1% and 3% of patients presenting with a suspected acute coronary syndrome (ACS) eventually are diagnosed as having TTC. There is a gender-specific prevalence, which is higher in women (6%–9%) than in men (<0.5%).
- In contrast to studies of true ACS, mean age, prehospital delay, and clinical symptoms, such as angina, are similar in male and female patients with TTC.
- Physical stress as a triggering event is more frequent in male patients with TTC, whereas emotional stress or no identifiable trigger is more prevalent in women.
- More male patients than female patients with TTC present with cardiogenic shock and/or out-of-hospital cardiac arrest; TTC, therefore, has to be considered as another important cause of sudden cardiac death, especially in men.
- There seems to be a disproportionate corrected QT (QTc) prolongation in male patients during the acute course of TTC predisposing men to malignant ventricular arrhythmias.
- The elevation of cardiac markers is higher in men. This may in part be related to physical stress as a trigger directly before the onset of TTC in men.
- The obvious female predominance of TTC is still not well understood. Further studies are necessary to clarify the pathogenetic background and develop strategies against this potentially life-threatening disease.

INTRODUCTION

TTC, first described in Japan in 1990, has increasingly been recognized in Western countries over the past years.[1–14] This cardiac syndrome mimics acute myocardial infarction (AMI) and is characterized by transient left ventricular regional dysfunction, ischemic ECG changes, and elevation of cardiac markers in the absence of significant coronary artery disease. Frequently, this reversible form of acute heart failure is precipitated by a stressful event. In all studies reported so far, there is a marked gender discrepancy in TTC, which affects predominantly elderly women.

Men and women with AMI are known to have a different clinical presentation and outcome[15–20] but currently there is little information about gender-related differences in the clinical profile of TTC.[21,22]

PATHOPHYSIOLOGIC BACKGROUND

The precise pathophysiology of TTC is still not well understood. As possible underlying mechanisms,

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transient multivessel coronary artery spasm,[1,23,24] coronary microvascular dysfunction,[25–29] and obstruction of the left ventricular outflow tract[5,8,9,30,31] due to a septal bulge have been proposed, all of which are more prevalent in women. The most widely accepted hypothesis suggests that TTC is caused by an excessive release of catecholamines after exposure to emotional or physical stress,[10,30,32] resulting in catecholamine-induced myocardial stunning.[33] Similar regional wall motion abnormalities have been observed in patients with high catecholamine levels due to pheochromocytoma[34,35] and subarachnoid hemorrhage.[36,37] Moreover, in a rat model of TTC, ST segment elevation and regional left ventricular dysfunction due to immobilization stress could be prevented by α-adrenoreceptor and β-adrenoreceptor antagonists.[38,39] Estrogen has a protective role on the cardiovascular system of postmenopausal women by attenuating catecholamine and glucocorticoid response to mental stress and by improving norepinephrine-induced vasoconstriction.[40,41] Thus, the reduction of estrogen levels after menopause may predispose elderly women to develop TTC[42–44] and can in part explain the striking female predominance of this syndrome.

EPIDEMIOLOGY

The exact incidence of TTC is unknown. Among patients presenting with a suspected ACS in Japan, the reported prevalence of TTC ranges from 1.2% to 2.2%.[2,45,46] In prospective studies from Western countries, between 2% and 3% of the patients undergoing coronary angiography because of suspected ACS eventually are diagnosed as having TTC.[47–51] There is a gender-specific prevalence that is higher in women, ranging from 6% to 9.8%, whereas the prevalence of TTC among male patients with an ACS is below 0.5%.[48–51]

DEMOGRAPHICS

Overall, 90% (range 65%–100%) of the patients with TTC are women.[52] In case series from Western countries, less than 11% are men.[8–14,22,25,27–29,31,47–51,53] The number of men seems higher in prospective studies from Asia, ranging from 13% to 35%.[5,7,21,30,32,45,54,55] This obvious female predominance of TTC is in contrast to patients with ACS.[15,16,18–20]

In several studies reported so far, the mean age has ranged from 62 to 76 years.[52] TTC is most frequently diagnosed in postmenopausal women over age 50 although premenopausal women and even children of both genders may be affected.[5,53,56–59] The mean age is similar in male patients and in female patients with TTC.[14,21,22,53] This finding is in contrast to studies of true ACS, where women are consistently 7 to 9 years older than men.[15,16,18,20]

TRIGGERING EVENTS

In the majority of patients (70%–80%), the onset of TTC is preceded by a triggering event, with a similar distribution of emotional and physical stress in 30% to 40% of the patients, respectively.[52] In the largest study of gender differences reported so far,[22] physical stress (most commonly, acute noncardiac illness or surgical/diagnostic procedure) was significantly more frequent in male patients with TTC (57% vs 30%, $P = .005$) whereas emotional stress or no identifiable trigger were more prevalent in women (**Table 1**). These findings are in accordance with 2 smaller studies,[21,53] where physical stress was also found the predominant stressor in men.

PREHOSPITAL DELAY

The time interval from symptom onset to hospital admission reported in TTC patients ranges from median 2 (interquartile range 1–5) up to 10 ± 16 hours.[9,10,13,60] In a study evaluating gender differences in TTC,[22] prehospital delay was 7.5 ± 6.9 hours and comparable in women and men (see **Table 1**). In contrast, patients with an ACS enrolled in a similar hospital setting had a shorter prehospital delay, which was significantly longer in female patients than in male patients (median 6.2 vs 5.1 hours for non–ST elevation myocardial infarction and median 3.3 vs 2.5 hours for ST elevation myocardial infarction; both $P<.001$).[16,18] These data imply that in patients with TTC symptoms may be less severe than in ACS, have a more insidious onset, and often are attributed by both male and female patients to the triggering event preceding TTC onset.

SYMPTOMS

The most common presenting symptoms in TTC are chest pain and dyspnea, which have been reported in 70% and 20% of the patients, respectively.[52] Initial presentation with syncope, nausea and vomiting, cardiogenic shock, and ventricular fibrillation, however, has also been observed.[4–6,8–10,13,27,45,46,53–57,60]

When comparing female patients and male patients with TTC,[22] chest pain was reported more frequently in women (73% vs 57%, $P = .08$) whereas dyspnea, syncope, and no or other diverse symptoms occurred with similar frequency