

Influence of Age and Gender in Takotsubo Syndrome



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KEYWORDS

- Takotsubo syndrome • Gender-related difference • Emotional stress • Physical stress
- QT prolongation • Ventricular tachycardia • Resuscitation • Apical ballooning syndrome

KEY POINTS

- There is a marked gender preference in Takotsubo syndrome (TTS), 90% of cases are females (mean age, 62 to 76 years). However, younger individuals and even children may also develop TTS.
- In contrast with studies with a “true” acute coronary syndrome, mean age, prehospital delay, and clinical symptoms are similar in male and female patients.
- Physical stress as a triggering event is more frequent in male patients, whereas emotional stress or no identifiable trigger are more prevalent in women.
- The elevation of cardiac markers is higher in males, which may be related to physical stress as a trigger directly before the onset of TTS in men.
- Further studies are necessary to clarify the pathogenetic background and develop strategies against this potentially life-threatening disease.

INTRODUCTION

Many features of Takotsubo syndrome (TTS) have puzzled doctors trying to understand the pathophysiology of this entity, which was first described in Japan in 1990.¹ One of these features is the overwhelming preponderance of women. Moreover, this is a disease mainly of elderly postmenopausal women; younger women seem to be only occasionally affected. In all studies reported so far, there is this marked gender discrepancy, although small numbers of males have also been described.^{1–13}

This review summarizes the current knowledge on the epidemiology and clinical presentation of TTS, focusing on age and gender.

PATHOPHYSIOLOGIC BACKGROUND

The precise pathophysiology of TTS and its gender preference are still not well-understood. As

possible underlying mechanisms, transient multi-vessel coronary artery spasm,^{1,14,15} coronary microvascular dysfunction,^{16–20} and obstruction of the left ventricular (LV) outflow tract^{4,7,8,21,22} owing to a septal bulge have been proposed, all of which are more prevalent in women. The most widely accepted hypothesis suggests that TTS is caused by an excessive release of catecholamines after exposure to emotional or physical stress,^{8,21,23} resulting in catecholamine-induced myocardial stunning.²⁴ Similar regional wall motion abnormalities have been observed in patients with high catecholamine levels owing to pheochromocytoma.^{25,26} The reason why females should respond more intensely to such stimuli is unknown, but the greater prevalence of microvascular abnormalities in females may play an important role. Estrogen may have a protective role on the cardiovascular system of postmenopausal females by attenuating catecholamine and glucocorticoid response to mental stress

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and by improving norepinephrine-induced vasoconstriction,^{27,28} although there are no clinical data confirming a protective effect of hormone replacement therapy against the occurrence of TTS.²⁹ The reduction of estrogen levels after menopause may predispose elderly women to develop TTS^{30–32} and can in part explain the striking female predominance of this syndrome.

EPIDEMIOLOGY AND DEMOGRAPHICS

The true incidence of TTS is unknown. There are most likely minor forms of this syndrome that are not severe enough to result in hospital admission; however, there may also be severe forms of TTS leading to death before the patient can reach the hospital. Approximately 1% to 3% of all patients with a suspected acute coronary syndrome (ACS) undergoing coronary angiography are diagnosed with TTS.^{16,33–37} There is a gender-specific prevalence that is higher in women, ranging from 6% to 9.8%, whereas the prevalence of TTS among male patients with an ACS is less than 0.5%.^{35–37} It is estimated that there are approximately 50,000 to 100,000 TTS cases per annum in the United States, with similar estimated numbers in Europe.^{38,39}

The majority (90%) of individuals with TTS are elderly postmenopausal women with a mean age of 67 years.^{3,11–13,38–41} The distribution of females and males in major studies is shown in **Table 1**. In case series from Western countries, less than 11% of the patients are men. The number of men, however, seems to be higher in prospective studies from Asia ranging from 13% to 35%.^{3,42,43}

AGE

Although the average age of patients with TTS is around 65 years, approximately 10% of the patients are less than 50 years of age,^{3,13} and even young individuals as well as children of both genders may be affected. Several studies look into the gender-specific age distribution of patients with TTS.^{13,40,43–45} In most reports, TTS occurs in both sexes at a similar age. However, females were found to be significantly older in 2 studies.^{13,43} This may be explained by the fact that up to 21% of the male patients included into these registries also had coronary artery disease where male patients are known to be consistently 7 to 9 years younger than females.^{46,47}

Older Age

Elderly patients (≥ 75 years of age) are considered to be at a greater risk of developing TTS and related major complications (**Box 1**). They experience more in-hospital composite adverse events and a higher in-hospital mortality (6.3% vs 2.8%). In this patient population, a higher frequency of acute heart failure and a longer time to recovery of LV function has also been reported. In addition, right ventricular involvement is more frequently seen in elderly patients as well as thrombus formation and a higher rate of stroke.^{13,48–50}

Younger Age

There are some case reports of younger females experiencing TTS in the context of normal pregnancy,⁵¹ after miscarriage, and after labor or delivery.^{52–55} The postpartum period may be at

Table 1
Age and gender in Takotsubo syndrome

Author, Year	Country	No. of Patients	Age (y)	Female (%)	Male (%)
Tsuchihashi et al, ³ 2001	Japan	88	67 ± 13	86	14
Song et al, ⁴² 2012	Korea	137	59 ± 12	74	26
Murakami et al, ⁴³ 2015	Japan	368	76 ± 9	77	23
Elesber et al, ⁹ 2007	USA	100	66 ± 13	95	5
Regnante et al, 2009 ⁷⁹	USA	70	67 ± 11	95	5
Sharkey et al, ⁴⁰ 2010	USA	136	68 ± 13	96	4
Schneider et al, ¹¹ 2010	Germany	324	68 ± 12	91	9
Parodi et al, ³⁷ 2011	Italy	116	73 ± 10	91	9
Eitel et al, ¹² 2011	Germany	256	69 ± 12	89	11
Citro et al, ⁴⁸ 2012	Italy	190	66 ± 11	92	8
Chong et al, 2012 ⁸⁰	Australia	80	68 ± 12	97	3
Schultz et al, 2012 ⁸¹	Sweden	115	64 ± 11	86	14
Templin et al, ¹³ 2015	Europe, USA	1750	67 ± 13	90	10

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