Influence of Genetics and Gender in Takotsubo Syndrome: Unexplored Areas of an Incompletely Understood Disease

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Abstract

Stress cardiomyopathy, also known as “Takotsubo syndrome” (TS), is a complex disease that typically affects postmenopausal women. The pathophysiology is still largely unknown, but evidence of a frequent association between TS and stressful events has evoked the hypothesis of a pathophysiologic role of sympathetic overdrive in the myocardial dysfunction. However, despite several studies, the role gender plays in TS onset remains unclear because stress cardiomyopathy also has been described in young women and in men. Moreover, although several cases of a familial cluster of TS have been reported, no responsible gene mutations or polymorphisms have been clearly identified so far, and neither the modality of transmission or the true impact of genetic background. In this review, we discuss the role of gender in the onset, course, and outcomes of TS and we report the available data about polymorphisms and gene mutations so far investigated, trying to critically analyze the evidence reported in the literature.

Keywords: Takotsubo, genetics, gender, stress cardiomyopathy

Introduction

Stress cardiomyopathy, also known as “Takotsubo syndrome” (TS), takes its name from a traditional Japanese globular, narrow-necked octopus trap called a “Takotsubo,” the shape of which the left ventricle (LV) takes on as a result of wall motion abnormalities typically involving the apex and midventricular segments; indeed, the LV takes on the appearance of an apical balloon, with a narrow neck and globular lower portion.1

TS usually affects postmenopausal women experiencing an emotionally stressful event that can be either a positive or negative experience. Referred symptoms are chest pain, sweating, dyspnea, and fatigue; electrocardiography (ECG) usually shows new and reversible abnormalities, including ST-segment elevation and/or T-wave inversion. Laboratory tests such as serum natriuretic peptide and cardiac troponin can be increased, mimicking an acute myocardial infarction, although there is no obstructive coronary artery disease seen on coronary angiography.

Echocardiography is a fundamental diagnostic tool in the evaluation of TS patients. It usually shows LV apical and circumferential midventricular hypokinesia and basal hypercontractility, with the typical apical ballooning at end-systole. This phenotype accounts for 50–80% of cases, and some less common variants can be observed, including the so-called inverted takotsubo or basal variant, with circumferential basal hypokinesia and apical hypercontractility; the mid-LV variant, with circumferential midventricular hypokinesia and both basal and apical hypercontractility; and rarer variants such as biventricular apical dysfunction, dysfunction sparing the apical tip, and isolated right ventricular syndrome (Table 1).2

TS pathophysiology is still largely unknown. Several hypotheses have been proposed, including aborted myocardial infarction caused by transient coronary artery occlusion, coronary spasm, and microvascular dysfunction; LV outflow tract obstruction, and catecholamine-mediated cardiac toxicity. The latter currently is the most accredited theory. Indeed, the evidence of a close relationship between physically or emotionally stressful events and TS onset, the finding of elevated serum catecholamine levels in patients presenting with TS,3 and the observation that the incidental administration of epinephrine at suprapharmacological doses4,5 or the excessive catecholamine production in patients with pheochromocytoma6 causes TS seem to suggest a strong role of sympathetic overdrive in the myocardial dysfunction.

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Moreover, the harmful effect of too-high levels of catecholamine on the heart has been confirmed in animal models, in which extensive myocyte necrosis and apoptosis and cardiac lipotoxicity have been reported. The particular distribution of wall motion abnormalities has been explained by the higher density of beta-adrenergic receptors (ARs) in the LV apex than in the base, which determines a greater susceptibility of the apical myocardium in comparison with basal segments to circulating catecholamines. In addition, the typical transience of LV systolic function seems to find a correspondence in the evidence of an increased activation of antiapoptotic genes, such as NFkB1 and BCL2, induced by catecholamines, which promote cell survival and protein biosynthesis, reducing the harmful effects on the heart.

Because LV systolic abnormalities are usually transient, TS generally has been considered a relatively benign disease. However, in recent years, it has been reported that about 50% of patients experience complications, including acute heart failure, cardiogenic shock, ventricular arrhythmias, and stroke due to thrombus formation in the LV apex, with a 5-year prognosis similar to that of myocardial infarction.

Pharmacological therapy is suggested only in patients with a high risk of severe complications; no drugs are needed in low-risk patients.

**Do Genetic Polymorphisms Play a Significant Role in TS Onset?**

TS is not commonly considered a primary genetic disease, but because of some familial cases describing TS aggregation in sisters or in mother and daughter, it has been speculated that genetic background may play an important role. However, these reports are limited, and so far no responsible gene mutations or modality of transmission has been clearly identified. Several gene polymorphisms have been investigated, including genes encoding for ARs and their intracellular signaling pathway (G-protein-coupled receptor kinase [GRK] 5, protein kinase A [PKA], beta arrestins), because sympathetic overdrive seems to have a close relationship with TS onset.

In physiological conditions, catecholamines bind β1 and β2 ARs on the myocyte membrane and couple to Gs (stimulation) protein complex; when activated, Gs proteins increase intracellular cyclic AMP levels through adenylyl cyclase, activating PKA, which phosphorylates several downstream intracellular targets, resulting in a positive inotropic response. In the presence of too-high levels of catecholamines, two main changes occur: β1ARs Gs protein signaling starts to induce apoptotic pathways in the cardiomyocytes and there is a switch in β2ARs coupling from Gs (stimulation) to Gi (inhibition) protein signaling. β2ARs Gi pathways have been shown to cause a negative inotropic effect on myocytes but have a protective role against apoptosis, balancing the overactivation of β1ARs Gs signaling.

At the same time, catecholamines induce the activation of GRK, which induces phosphorylation of βARs and binding with β-arrestins, proteins that inhibit the inotropic effects of βARs. The result, if the binding is prolonged, is decreased cardiac function. Moreover, GRK induces G-protein uncoupling with the shut-off of the signal induced by catecholamines.

The aim of these self-limiting processes, called “βAR desensitization,” is to protect the heart from prolonged or chronic sympathetic stimulation. Finally, when catecholamine levels come back into normal ranges, β2ARs coupled to Gi proteins switch back to Gs protein coupling, allowing the recovery of myocardial function.

Although several authors have tried to investigate the role of these mutations in TS pathophysiology, the results are ambiguous so far. Polymorphisms of ARs, the substitution of a glycine with an arginine in β1AR (Gly389Arg), and the presence of a glutamic acid instead of glutamine in β2AR (Gln27Glu) have been reported; these polymorphisms seem to be associated with increased agonist activity of catecholamines, enhanced cardiac catecholamine sensitivity, and increased cardiac vulnerability to adrenergic stress determining an increased susceptibility to TS.

Moreover, the same mutations have been correlated with cardiac dysfunction attributed to post-subarachnoid hemorrhage-induced catecholamine surge, reinforcing the hypothesis of their pathophysiological role. However, these postulated causes are not confirmed in several other studies, which did not report significant differences in the frequency of β1 and β2-AR polymorphisms between TS patients and controls. Interestingly, Goodloe
et al. performed a whole-exome sequencing to comprehensively genotype 28 TS patients. The authors were able to investigate a vast, 486-gene network for adrenergic signaling and found that the frequencies of 17 common, functional adrenergic polymorphisms, including ones already cited, were similar between patients and controls. However, two-thirds of TS patients carried more than one adrenergic pathway variant and 11 genes harbored a variant in 2 cases, suggesting a genetic heterogeneity in TS susceptibility and a likely polygenic basis that confers a cumulative effect on adrenergic pathway dysregulation in these subjects.

Similar contradictions can be underlined in the studies that investigated the role of polymorphisms of the main proteins involved in the βARs intracellular signaling pathway, including GRKs. The substitution of a glutamine with a leucine in GRK5 (Gln41Leu), one of the main types of GRKs in the myocardium, was reported by Novo et al. and Spinelli et al. to be significantly different in patients with TS than in controls; this polymorphism seems to increase the physiological process of βARs desensitization, reducing the inotropic function of the LV apex, where βARs are more represented, and contributing to the onset of apical ballooning. However, these findings were not confirmed by Fittree et al., who evaluated a large cohort of Australian patients with TS, nor by Goodloe et al. in their comprehensive analysis of the genes involved in adrenergic signaling in 28 patients.

These apparent contradictions about the role of ARs and GRK polymorphism possibly could be explained by the differences in race and width of the cohorts evaluated (Table 2).

Vriz et al. studied a population of 96 Caucasian patients, but their results could not be replicated in other Caucasian, but significantly smaller, cohorts or in a large Australian cohort; similarly, the GRK5 polymorphism has been

### Table 2. Comparison Between Cohorts Investigated for Presence of β-Adrenergic Receptor Polymorphisms

| Authors       | Protein name | Protein mutation | Population | No. of patients | Gender (female, %) | Findings                                                                 |
|---------------|--------------|------------------|------------|-----------------|--------------------|-------------------------------------------------------------------------|
| Vriz et al.²⁰ | β1 ARs       | Gly389Arg        | Italian    | 61              | 96                 | Mutations significantly more frequent in patients with TS compared with controls |
|               | β2 ARs       | Gln27Glu         |            |                 |                    |                                                                         |
| Vriz et al.²¹ | β1 ARs       | Gly389Arg        | Italian    | 97              | 96                 | Significant differences between TS and controls but not between TS and STEMI patients |
|               | β2 ARs       | Gln27Glu         |            |                 |                    |                                                                         |
| Sharkey et al.²³ | β1 ARs | Arg389Arg arg389Gly | Hispanic  | 41              | 100                | No significant differences between TS and controls                      |
|               |              | Gly389Gly        |            |                 |                    |                                                                         |
|               |              | Ser49Ser         |            |                 |                    |                                                                         |
|               |              | Ser49Gly         |            |                 |                    |                                                                         |
|               |              | Gly49Gly         |            |                 |                    |                                                                         |
|               |              | Wt322—325Wt      |            |                 |                    |                                                                         |
|               |              | Wt322—325Del     |            |                 |                    |                                                                         |
| Fittree et al.²⁴ | β1 ARs | Gly389Arg        | Australian | 92              | 97                 | No significant differences between TS and controls                        |
|               | β2 ARs       | Gln41Leu         |            |                 |                    |                                                                         |
|               | GRK5         |                   |            |                 |                    |                                                                         |
| Spinelli et al.²⁵ | β1 ARs | Arg31Gln         | Italian    | 22              | 82                 | Gln41Leu polymorphism of GRK5 is significantly more frequent in TS patients than controls. No other significant differences between TS and controls |
|               |              | Ser49Gly         |            |                 |                    |                                                                         |
|               |              | Gly16Arg         |            |                 |                    |                                                                         |
|               | β2 ARs       | Gln27Glu         |            |                 |                    |                                                                         |
|               |              | Thr164Ile        |            |                 |                    |                                                                         |
|               |              | Gln41Leu         |            |                 |                    |                                                                         |
|               |              | Thr129Met        |            |                 |                    |                                                                         |
|               | GRK4         |                   |            |                 |                    |                                                                         |
|               | β3 ARs       | Trp64Arg         |            |                 |                    |                                                                         |
|               |              | Arg65Leu         |            |                 |                    |                                                                         |
|               |              | Ala142Val        |            |                 |                    |                                                                         |
|               |              | Ala486Val        |            |                 |                    |                                                                         |
|               |              | Gly41Leu         |            |                 |                    |                                                                         |
|               |              | Thr129Met        |            |                 |                    |                                                                         |
| Goodloe et al.²⁷ | β ARs | Cys347Arg        | North European | 28              | 97                 | No significant differences between TS and controls                        |
|               |              | Asn266Lys        |            |                 |                    |                                                                         |
|               |              | Del1222–325      |            |                 |                    |                                                                         |
|               | β1 ARs       | Arg31Gln         |            |                 |                    |                                                                         |
|               |              | Ser49Gly         |            |                 |                    |                                                                         |
|               |              | Gly389Arg        |            |                 |                    |                                                                         |
|               | β2 ARs       | Gly16Arg         |            |                 |                    |                                                                         |
|               |              | Gln27Glu         |            |                 |                    |                                                                         |
|               |              | Thr164Ile        |            |                 |                    |                                                                         |
|               | β3 ARs       | Trp64Arg         |            |                 |                    |                                                                         |
|               |              | Arg65Leu         |            |                 |                    |                                                                         |
|               |              | Ala142Val        |            |                 |                    |                                                                         |
|               |              | Ala486Val        |            |                 |                    |                                                                         |
|               |              | Gly41Leu         |            |                 |                    |                                                                         |
|               |              | Thr129Met        |            |                 |                    |                                                                         |
|               | GRK5         |                   |            |                 |                    |                                                                         |

ARs, adrenergic receptors; GRK, G-protein-coupled receptor kinase; STEMI, ST elevation myocardial infarction; TS, Takotsubo syndrome.
reported in small Italian cohorts\textsuperscript{18,25} but could not be confirmed in Australian and North American ones.\textsuperscript{24,27}

Moreover, Citro et al.\textsuperscript{28} described the presence of two single-nucleotide polymorphisms of the gene encoding for Bcl2-associated athanogene 3 (BAG3), a protein that supports muscle survival and contractile activity, mediates cell adaptive responses to stressful stimuli, and is involved in regulation of apoptosis. Genes involved in the survival cascade of myocytes and in increased protein biosynthesis are overexpressed in patients with TS, and their activation is fundamental for the fast recovery of cardiac function.\textsuperscript{29} The two missense mutations investigated (R71Q and P407L) seem to (1) interfere with the cardioprotective role of some members of the heat shock protein (HSP) family, a group of proteins with an important role in the response to oxidative stress and cell survival, and (2) reduce the availability of mediators of the release of intracellular calcium and calcium influx, favoring myocyte apoptosis.\textsuperscript{28}

These findings indicate a possible role of a genetic background in the onset of TS; however, the absence of multigenerational families with Mendelian inheritance of TS and the conflicting results obtained in different populations seem to suggest a gene/environment interaction, polygenic etiology, and/or recessive susceptibility alleles but not a dominant inheritance of a variant or variants of single genes with major effect, as already speculated.\textsuperscript{27}

**TS and Gender: Does It Really Matter?**

TS is commonly considered a gender-specific disease, affecting mainly women.\textsuperscript{5} All the studies have found very high percentages of female patients, ranging between 74\% and 97\%,\textsuperscript{30,31} and this trend has been confirmed by Brinjikji et al.,\textsuperscript{32} who analyzed the largest cohort of North American patients (more than 24,700 subjects), of whom 89\% were women. Conversely, higher percentages of men have been reported in studies involving Asian patients.\textsuperscript{31,33} There is not a satisfactory explanation for this discrepancy, except for the possibility of a different genetic background that could make Asian men more prone to the harmful effects of catecholamines than the general male population.

The influence of gender on the development of Takotsubo is one of the widest shadow areas that characterize this syndrome. It has been reported that women are more often affected by TS, usually after an emotional stress, but they have complications of mild relevance, whereas men who develop TS commonly do so after physical stress (surgical procedures, severe diseases, etc.) and more frequently experience cardiogenic shock, severe arrhythmias, pulmonary edema, and stroke.\textsuperscript{2,33,37}

No significant differences have been described with respect to age, symptoms, or complications. Instead, contradictory findings have been reported about outcomes and mortality in males and females. Most authors found a similar rate of mortality between the sexes,\textsuperscript{33–35,37} but some large studies\textsuperscript{11,32,36,38,39} reported a higher mortality for men. Murakami et al.\textsuperscript{33} indicated male gender as an independent predictor of adverse composite cardiac events, including cardiovascular death, severe pump failure, and serious ventricular arrhythmia. These discrepancies could possibly be due to an increased prevalence of severe comorbidities—such as acute critical illnesses like coronary syndrome, ventricular arrhythmia, and sudden cardiac arrest—in men; according to this hypothesis, the increased mortality would not be strictly correlated with TS, but would be a consequence of a more severe burden of comorbidities in male patients.

The most accepted theory is based on evidence that male patients show more severe and early complications of TS, which could prove fatal before medical care can be sought. These data show that caution is needed when considering TS a benign disease, at least in patients with severe comorbidities.

Interestingly, age seems to play an important role in the onset of TS, particularly in women. Indeed, elderly postmenopausal women are at greater risk of developing TS, although younger subjects—especially in the context of amphetamine abuse, cerebral disorders, anorexia nervosa, and pregnancy—can, not entirely infrequently, develop TS\textsuperscript{44} and cases have even been described in children and newborns.\textsuperscript{40} Moreover, young patients have a significantly higher rate of recurrence during follow-up but a relatively benign prognosis compared with older women.\textsuperscript{37}

Evidence of these significant differences in the prevalence of TS in women, particularly in postmenopausal subjects, and the lack of a similar correlation with age in men made several authors speculate that estrogens play a pathophysiological role in TS. The cardioprotective effects of estrogens include reduction of sympathoadrenal system activation, antioxidant effects, and vasodilatation; moreover, estrogens reduce the enhanced expression of \( \beta \)1ARs, favoring \( \beta \)2ARs signaling and thus protecting myocytes from apoptosis.\textsuperscript{17} Accordingly, it has been shown that rats with ovaries removed and estrogen supplementation had better cardiac function after stressful events than those without hormone administration.\textsuperscript{41} Similar findings have been obtained in a case series of postmenopausal women with TS.\textsuperscript{42}

In addition, a possible pathophysiological role of some polymorphisms of estrogen receptors \( \alpha \) and \( \beta \) genes (Cys397Thr and Gly1839Thr, respectively) that reduce estrogen effects has been postulated.\textsuperscript{43} However, recent data showed that TS occurred in postmenopausal women despite hormone replacement therapy,\textsuperscript{37} and that oophorectomized women did not evidence a worse clinical course,\textsuperscript{45} suggesting that hypoestrogenemia itself cannot be the primary cause of TS development, even if it probably plays a protective role. Moreover, men show low estrogen levels throughout their life, so the sudden decrease of estrogen could be an explanation for the postmenopausal development of TS in women, but cannot explain why females are significantly more prone to TS than males.

Some authors\textsuperscript{45} speculated that males could be biologically better protected against the stress-induced cardiotoxicity of catecholamines than females. This hypothesis seems to find some confirmation in the higher density of ARs in the membranes of cardiomyocytes in males than in females,\textsuperscript{46} which may imply that lower concentrations of catecholamines could saturate their receptors and cause the more detrimental effects on the LV, producing a negative inotropic response and myocyte apoptosis.

Another possible explanation is related to the higher frequency of death before hospital admission among male patients than female.\textsuperscript{45} According to this theory, a significant percentage of cardiac arrests usually ascribed to acute coronary syndromes could be due to stress cardiomyopathy,
which would then be underdiagnosed. However, this hypothesis does not seem to be particularly reliable, because the percentage of male patients with a diagnosis of TS is about 10%: if the percentage of males and females was the same and the difference in the registries was only due to the underdiagnosis of male patients who died before hospitalization, it would mean that TS is the most dangerous heart disease ever described.

Conclusions

TS is a complex disease whose pathophysiology is still largely unclear. Catecholamines probably play a substantial role in the development of the disease, and it is very likely that genetic alterations of members of the complex net of intracellular signaling pathways involved in the regulation of catecholamine effects on myocytes could be responsible for the increased susceptibility of some subjects over others. However, the genetic heterogeneity and a likely polygenic basis probably confer a cumulative effect on adrenergic pathway dysregulation, which determines a continuous spectrum of susceptibility to TS and can significantly differ from subject to subject; thus, a comprehensive evaluation of genetic profile—and not the identification of pathognomonic genetic mutations—seems to be the most reasonable approach.

Gender has an important influence in the clinical features of the disease, and estrogen levels and genetic alterations of estrogen signaling pathways may play a significant role in the regulation of catecholamines’ effects. These probably are other pieces of the puzzle that should be considered in the evaluation of the single patient risk profile.

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