

Editorial

Do Male Hearts Break Differently?

¿Cómo se les rompe el corazón a los hombres?

Birke Schneider^{a,*} and Udo Sechtem^b^a Medizinische Klinik II, Sana Kliniken Lübeck, Kahlhorststrasse 17, D-23562, Lübeck, Germany^b Abteilung für Kardiologie, Robert-Bosch-Krankenhaus, Auerbachstrasse 110, D-70376, Stuttgart, Germany

Article history:

Available online 21 March 2018

Tako-tsubo syndrome (TTS), initially reported in Japan in 1990, is an acute heart failure syndrome that has increasingly been recognized worldwide over the last few years due to heightened awareness of its existence. The clinical presentation resembles an acute coronary syndrome and left ventricular angiography shows systolic dysfunction usually of the apical and midventricular segments; however, obstructive coronary artery lesions explaining the regional wall motion abnormality are absent. Frequently, manifestation of TTS is preceded by a triggering event consisting of either emotional or physical stress. There is a marked sex preference since most (90%) of individuals with TTS are elderly postmenopausal women with a mean age of 65 to 70 years.¹ In most case series from Western countries, less than 12% of the patients are men.^{1–9} The number of men, however, seems to be higher in studies from Asia, ranging from 13% to 35%.^{10–13} Tako-tsubo syndrome has generally been regarded as a relatively benign disease with rapid recovery of left ventricular dysfunction. However, growing evidence suggests it is a more serious cardiac disorder with a variety of complications, such as acute heart failure, cardiogenic shock, malignant arrhythmias, left ventricular outflow tract obstruction, mitral regurgitation, right ventricular involvement with pleural effusion, thrombus formation resulting in stroke and arterial embolism, pericardial effusion, and ventricular wall rupture.¹ Overall, in-hospital mortality has been reported in 2% to 7% of TTS patients.^{2–4,6–13} Secondary forms of TTS triggered by physical stress and occurring in patients already hospitalized for another serious medical condition are associated with an even higher mortality rate, ranging from 10% to 21%.^{3,7,12–15}

One still poorly understood aspect of TTS is the obvious female preponderance. Besides pathophysiological differences in the cardiovascular system, such as the higher prevalence of microvascular abnormalities predisposing women to develop TTS,¹ it is currently unclear whether underdiagnosis or misdiagnosis may contribute to the apparently lower prevalence of TTS in men. Another reason for underestimating the prevalence of TTS in men could be that they more often die suddenly in the early phase of TTS and the diagnosis cannot be established because the typical course of this syndrome with rapid resolution of the wall abnormality cannot be documented. The fact that men more

frequently arrive at hospital after resuscitation indicates a greater electrical vulnerability in the early phase of TTS.^{4,6}

In this context, a recent article published in *Revista Española de Cardiología* by Pérez-Castellanos et al. evaluated sex differences in the RETAKO registry, focusing mainly on complications and prognosis. Between 2003 and 2015, 562 patients from 32 Spanish hospitals with a diagnosis of TTS according to the modified Mayo criteria had been included in the registry.⁹ The mean age was 69.5 ± 14.5 years, and 493 patients (87.7%) were women. Chest pain as the presenting symptom was significantly more frequent in women and syncope was more frequent in men, and more men were current smokers. These findings are well in accordance with previous studies in other Western countries.^{4,6,15} Regarding age, additional cardiovascular risk factors, baseline functional class, electrocardiogram findings, and left ventricular ejection fraction, no significant differences were found between the sexes. During the clinical course, left ventricular outflow tract obstruction and mitral regurgitation of moderate to severe degree, in part due to systolic anterior motion of the mitral leaflet, was seen more frequently in women. This contrasts with the results of 3 studies from Germany and Japan, where the frequency of left ventricular outflow tract obstruction was similar in male and female patients.^{4,10,11} Possibly, these findings may have been influenced by other factors, such as the use of inotropic drugs, nitrates, or different premedication with diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. In the RETAKO registry, other complications such as severe heart failure and cardiogenic shock occurred significantly more often in men and resulted in a longer stay in the intensive care unit. In the literature, there are conflicting results, since some studies found no significant sex difference regarding cardiogenic shock,^{4,6,8} whereas others reported a significantly higher prevalence in men.^{3,11} Overall, in-hospital mortality in the RETAKO registry was low (0.7%) but was higher in men than in women (4.4% vs 0.2%, $P < .01$). However, secondary TTS, known to be associated with a worse prognosis, was significantly more frequent in male patients and may in part be responsible for the higher mortality rate in men. Similarly, a meta-analysis of 37 studies¹¹ and evaluation of the United States National Inpatient Database³ found significantly higher in-hospital mortality in men. In these studies, the presence of underlying critical illness was

SEE RELATED CONTENT:

<https://doi.org/10.1016/j.rec.2017.07.021>, *Rev Esp Cardiol.* xxxx;xx:xx-xx* Corresponding author: Medizinische Klinik II, Sana Kliniken Lübeck, Kahlhorststrasse 17, D-23562 Lübeck, Germany.
E-mail address: birke.schneider@t-online.de (B. Schneider).<https://doi.org/10.1016/j.rec.2018.02.013>

1885-5857/© 2018 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

the main driver of mortality and most likely explained the higher mortality rate among men. The InterTAK registry⁶ also reported significantly higher mortality in men. However, in a multivariate analysis including a physical trigger as a covariate, sex was no longer a significant predictor of worse outcome. Moreover, multivariate analysis in a study of 3719 patients with TTS from the Diagnosis Procedure Combination database in Japan showed that secondary TTS and old age but not male sex was associated with an increase in in-hospital mortality.¹² In addition, male patients with TTS not only suffer from acute medical illnesses more frequently than women, but they also have more chronic comorbidities such as cancer,^{8,13} chronic obstructive pulmonary disease,^{6,8,13} and bystander coronary artery disease,^{6,8,12} which is *per se* associated with a worse prognosis.¹⁶

Do male hearts break differently? Overall, male patients with TTS seem to have a more severe clinical background with a higher frequency of both chronic comorbidities and acute illnesses, which determine clinical outcome. Whether “lone” TTS has indeed a worse prognosis in men than in women remains to be determined in a large prospective study.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Lyon AL, Bossone E, Schneider B, Sechtem U, et al. Current state of knowledge on takotsubo syndrome: a position statement from the task force on takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2016;18:8–27.
2. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol.* 2010;55:333–341.
3. Brinjikji W, El-Sayed AM, Salka S. In-hospital mortality among patients with takotsubo cardiomyopathy: a study of the National Inpatient Sample 2008 to 2009. *Am Heart J.* 2012;164:215–221.
4. Schneider B, Athanasiadis A, Stöllberger C, et al. Gender differences in the manifestation of tako-tsubo cardiomyopathy. *Int J Cardiol.* 2013;166:584–588.
5. Mhadavan M, Rihal CS, Lerman A, et al. Acute heart failure in apical ballooning syndrome (takotsubo/stress cardiomyopathy). *J Am Coll Cardiol.* 2011;57:1400–1401.
6. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med.* 2015;373:929–938.
7. Nunez-Gil IJ, Almenro-Delia M, Andres M, et al. Secondary forms of takotsubo cardiomyopathy: a whole different prognosis. *Eur Heart J Acute Cardiovasc Care.* 2016;5:308–316.
8. Weidner KJ, El-Battrawy I, Behnes M, et al. Sex differences of in-hospital outcome and long-term mortality in patients with takotsubo cardiomyopathy. *Therapeutics Clin Risk Management.* 2017;13:863–869.
9. Pérez-Castellanos A, Martínez-Sellés M, Mejía-Rentería H, et al. Takotsubo syndrome in men: rare but with poor prognosis. *Rev Esp Cardiol.* 2018;71:703–708.
10. Kurisu S, Inoue I, Kawagoe T, et al. Presentation of tako-tsubo cardiomyopathy in men and women. *Clin Cardiol.* 2010;33:42–45.
11. Murakami T, Yoshikawa T, Maekawa Y, et al. Gender differences in patients with takotsubo cardiomyopathy: multi-center registry from Tokyo CCU Network. *PLoS ONE.* 2015;10:e0136655.
12. Isogai T, Yasunaga H, Matsui H, et al. Out-of-hospital versus in-hospital takotsubo cardiomyopathy: analysis of 3719 patients in the diagnosis procedure combination database in Japan. *Int J Cardiol.* 2014;176:413–417.
13. Sobue Y, Watanabe E, Ichikawa T, et al. Physically triggered takotsubo cardiomyopathy has a higher in-hospital mortality rate. *Int J Cardiol.* 2017;235:87–93.
14. Singh K, Carson K, Dip LM, et al. Meta-analysis of clinical correlates of acute mortality in takotsubo cardiomyopathy. *Am J Cardiol.* 2014;113:1420–1428.
15. Patel SM, Chokka RG, Prasad K, Prasad A. Distinctive clinical characteristics according to age and gender in apical ballooning syndrome (takotsubo/stress cardiomyopathy): an analysis focusing on men and young women. *J Cardiac Fail.* 2013;19:306–310.
16. Bill V, El-Battrawy I, Schramm K, et al. Coincidental coronary artery disease impairs outcome in patients with takotsubo cardiomyopathy. *QJM.* 2017;110:483–488.