ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–3
https://doi.org/10.1093/ehjcr/ytac235

EDITORIAL

The Swiss cheese model in takotsubo syndrome

Luca Arcari [1]*, Maria Beatrice Musumeci[2], and Luca Cacciotti[1]

[1]Cardiology Unit, Madre Giuseppina Vannini Hospital, Rome, Italy; and [2]Cardiology, Clinical and Molecular Medicine Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy

Online publish-ahead-of-print 10 June 2022

This editorial refers to "A case report of recurrent takotsubo cardiomyopathy including the rare 'inverted' form", by Charles Carey *et al*. https://doi.org/10.1093/ehjcr/ytac207.

Holes in the cheese, flaws in the plan

In 1990, James Reason of Manchester University designed a model, which later came to be popularly known as the 'Swiss cheese model', to provide a framework for the understanding of the dynamics underlying accident causation within complex systems, such as those occurring in nuclear power plants, chemical installations or spacecrafts.[1] The final event, he hypothesized, could be explained by a large number of causative factors, all necessary but not able to generate the outcome on their own: the system breakdown ensues from latent failures combined with triggering conditions that overcome the system's defences.[1] At about the same time, in Japan, a novel cardiac syndrome was reported for the first time: it was characterized by infarct-like presentation, mid-apical left ventricular (LV) dyskinesia, patent coronary arteries, and LV contractility recovery at follow-up.[2] This clinical condition was named 'takotsubo syndrome' (TTS), to highlight the similarity of the LV shape in the acute phase with the Japanese pot (takotsubo) traditionally used for fishing octopus. More than three decades later, a complete understanding of TTS pathophysiology is still lacking, and the 'Swiss cheese model' appears to be a useful abstraction to represent the events leading to a TTS attack (*Figure 1*). Indeed, TTS is often characterized by triggering conditions preceding the onset,[3] either emotional, physical or both,[4] coupled with a chronic vulnerable background.[5] This latter is composed of comorbidities, genetic predisposition, hormonal, and psychosocial factors among others,[3] which, together, impair the ability of safely managing stressful triggers and contribute to the development of cardiac involvement.

Takotsubo recurrence—the role of case reports

One of the most intriguing aspects of the syndrome is that, despite the reiterative exposure to various stressful triggers in daily life, it occurs uncommonly and rarely recurs, even in highly susceptible individuals. A comprehensive assessment of TTS recurrences is therefore essential, especially in those few outliers presenting with more than two events, for its potential in helping us to uncover its physiopathology. Recently, two of the largest, multicentric, international registries to date, provided an analysis of TTS recurrences. The GEIST[6] and the InterTAK[7] registries reported a prevalence of 4–5% within their populations, with a recurrence rate of ∼2% patients-year. In both these studies' findings, ballooning patterns often varied between episodes, while pre-existing predisposing conditions such as comorbidities (e.g. psychiatric diseases and hypertension) remained associated with TTS recurrence, a results that is in keeping with others.[8,9] However, even in multicentric registries the population with recurrent TTS, especially those with multiple recurrences, remains relatively small, making case reports a valuable tool to explore more in detail the features of these patients. In the present issue of *European Heart Journal - Case Reports*, Carey *et al*. describe the case of a woman experiencing multiple TTS recurrences, the second one presenting with the uncommon basal contraction pattern, providing an insightful diagnostic confirmation by means of cardiac magnetic resonance tissue mapping imaging.[10] Consistently with registry data, the patient had several comorbidities including previous meningioma excision, hypertension and irritable bowel syndrome; of note, her clinical history included

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal- Case Reports* or of the European Society of Cardiology.

* Corresponding author: Tel: +390624291542; Email: luca_arcari@outlook.it

Handling Editor: Amardeep Ghosh Dastidar

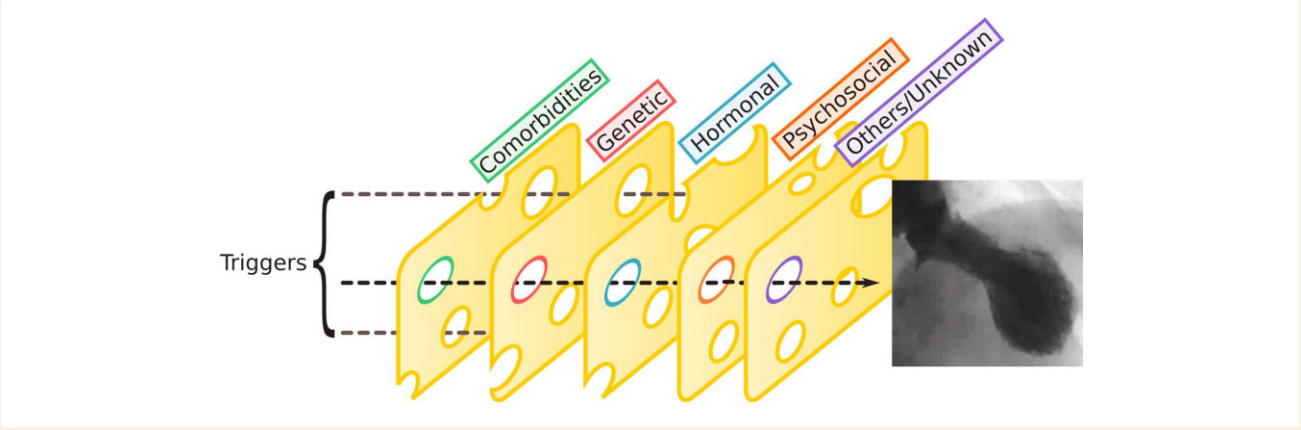

Figure 1 Graphical representation of the 'Swiss cheese model' applied to TTS. Protective mechanisms (slices) reduce the systemic consequences of stressful triggers. In vulnerable individuals, several factors (holes) impair the patients' ability to manage triggers, favouring the development of myocardial wall motion abnormalities. In some patients, specific combinations of reiterative triggers with chronic failures in certain protective layers may enhance TTS recurrence. The presence of unknown factors/failing protective mechanisms prevent us a full understanding of the underlying pathogenesis.

chronically high levels of emotional stress and anxiety, with emotional distress preceding at least the first event. The *Journal* recently published two more case reports that could meet this same clinical picture, with multiple TTS recurrences affecting women and preceded, when identifiable, by a trigger of emotional nature.[11,12]

Unfortunately, this classic phenotype is not always seen and only partly encompasses the heterogeneous and enlarging clinical spectrum of TTS. A unifying pattern is far from being established, as highlighted by the observation of a recurrent TTS in a male patient with underlying pulmonary disease and physical trigger[13] who experienced, as more common in males,[14] a fatal outcome at follow-up. Takotsubo syndrome recurrences can take place in the setting of pheochromocytoma too: Sato *et al.*[15] describe the case of a patient who had multiple TTS events, with both epicardial and microvascular coronary spasm, before the neoplasm was finally identified and removed. Even more striking is the case reported by Hiruma *et al.*,[16] where a 79-year-old woman experienced four episodes of TTS in the short time period of 10 months, with extremely variable triggering conditions and ballooning presentation, making it impossible to hypothesize any recurrent pattern.

Conclusions

All these reports together certify our incomplete knowledge on the topic, albeit suggesting how, at least in some cases, TTS recurrences might be associated with the activation of reiterative pathogenic pathways, facilitated by the persistence of latent failures in certain protective mechanisms in example signified by underlying psychological and social factors,[17] large comorbid burden, or catecholamine-producing tumours. What we still lack is the full understanding of these pathways, as well as of the reason why their activation can sometimes be apparently unprovoked, or even follow certain stressful triggers but not others. Accordingly, the 'Swiss cheese model' fails to completely represent the unclear TTS pathogenic background, where the uncomplete knowledge of all the failing protective layers prevents us to have a clear view of its pathogenesis even after the event has occurred. To this extent, one limitation of the reports discussed previously is the absence of an assessment of the brain–heart axis[18] in the first as well as recurrent episodes; indeed, it could be of interest to know whether similar/different clinical presentations between the index and recurrent event correspond to similar/different patterns of brain–heart activation.[19] Future studies on recurrent TTS should pursue the aim of a comprehensive patients' characterization, to identify reiterative patterns of TTS onset. This could be instrumental to a definition of different TTS phenotypes, with their own clinical features and possibly only partly shared physiopathology, contributing to shed more light into the mechanisms of this fascinating and still poorly understood disease.

Lead author biography

Dr. Luca Arcari is consultant cardiologist at the Cardiology unit of Madre Giuseppina Vannini Hospital in Rome, Italy. His research interest is focused on cardiovascular imaging of hypertrophic and infiltrative cardiomyopathies, uremic phenotypes and takotsubo syndrome.

Acknowledgements

We thank Gabriele Arcari, MD, for designing the illustration depicted in Figure 1.

Conflict of interest: None declared.

Funding: None declared.

References

1. Reason J. The contribution of latent human failures to the breakdown of complex systems. *Philos Trans R Soc London B, Biol Sci* 1990;**327**:475–484.
2. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol* 1991; **21**: 203–214.
3. Omerovic E, Citro R, Bossone E, Redfors B, Backs J, Bruns B, Ciccarelli M, Couch LS, Dawson D, Grassi G, Iacoviello M, Parodi G, Schneider B, Templin C, Ghadri JR, Thum T, Chioncel O, Tocchetti CG, van der Velden J, Heymans S, Lyon AR. Pathophysiology of Takotsubo syndrome - a joint scientific statement from the Heart Failure Association Takotsubo Syndrome Study Group and Myocardial Function Working Group of the European Society of Cardiology - Part 2: vascular pathophysiology, gender and sex hormones, genetics, chronic cardiovascular problems and clinical implications. *Eur J Heart Fail* 2021;**24**:274–286.
4. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss H-P, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck K-H, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KEJ, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF.. Clinical features and outcomes of takotsubo (Stress) cardiomyopathy. *N Engl J Med* 2015;**373**: 929–938.
5. Limite LR, Arcari L, Cacciotti L, Russo D, Musumeci MB. Cardiogenic Shock in Takotsubo Syndrome. *JACC Hear Fail* 2019; **7**:175–176.
6. El-Battrawy I, Santoro F, Stiermaier T, Möller C, Guastafierro F, Novo G, Novo S, Mariano E, Romeo F, Romeo F, Thiele H, Guerra F, Capucci A, Giannini I, Brunetti ND, Eitel I, Akin I. Incidence and clinical impact of recurrent takotsubo syndrome: results from the GEIST registry. *J Am Heart Assoc* 2019;**8**:e010753.
7. Kato K, Di Vece D, Cammann VL, Micek J, Szawan KA, Bacchi B, Lüscher TF, Ruschitzka F, Ghadri JR, Templin C. Takotsubo Recurrence. *J Am Coll Cardiol* 2019; **73**:982–984.
8. Nayeri A, Rafla-Yuan E, Farber-Eger E, Blair M, Ziaeian B, Cadeiras M, McPherson JA, Wells QS. Pre-existing psychiatric illness is associated with increased risk of recurrent takotsubo cardiomyopathy. *Psychosomatics* 2017;**58**:527–532.
9. Arcari L, Cacciotti L, Limite LR, Russo D, Sclafani M, Semeraro R, Ansalone G, Volpe M, Autore C, Musumeci MB. Clinical characteristics of patients with takotsubo syndrome recurrence: an observational study with long-tem follow-up. *Int J Cardiol* 2020;**329**:23–27.
10. Carey C, Macnab A, Nucifora G. A case report of recurrent takotsubo cardiomyopathy including the rare 'inverted' form. *Eur Hear J - Case Reports*:ytac207.
11. Chandy S, Dawson DK. Lifelong recurrent takotsubo cardiomyopathy: a case report. *Eur Hear J - Case Reports* 2019; **3**:1–5.
12. Nomura T, Sakaue Y, Ono K, Wada N. Five recurrent episodes of takotsubo syndrome provoked by various triggers over a period of 7 years: a case report. *Eur Hear J - Case Reports* 2021;**5**:ytab431.
13. Luo CEL, Kardos A. Case report: recurrent biventricular Takotsubo cardiomyopathy in a middle-aged man with fatal outcome after full recovery. *Eur Hear J - Case Reports* 2019; **3**:1–6.
14. Arcari L, Núñez-Gil IJ, Stiermaier T, El-Battrawy I, Guerra F, Novo G, Musumeci B, Cacciotti L, Mariano E, Caldarola P, Parisi G, Montisci R, Vitale E, Sclafani M, Volpe M, Corbì-Pasqua M, Martinez-Selles M, Almendro-Delia M, Sionis A, Uribarri A, Akin I, Thiele H, Brunetti ND, Eitel I, Santoro F. Gender differences in takotsubo syndrome. *J Am Coll Cardiol.* 2022;**79**:2085–2093.
15. Sato K, Takahashi J, Amano K, Shimokawa H, Memtsas VP. A case of recurrent takotsubo-like cardiomyopathy associated with pheochromocytoma exhibiting different patterns of left ventricular wall motion abnormality and coronary vasospasm: a case report. *Eur Hear J - Case Reports* 2020; **4**:1–5.
16. Hiruma T, Higuchi R, Iguchi N. Quadruple episodes of takotsubo cardiomyopathy: a case report. *Eur Hear J - Case Reports* 2021; **5**:ytaa574.
17. Casagrande M, Forte G, Favieri F, Agostini F, Giovannoli J, Arcari L, Arcari L, Passaseo I, Semeraro R, Camastra G, Langher V, Pazzaglia M, Cacciotti L. The broken heart: the role of life events in takotsubo syndrome. *J Clin Med* 2021;**10**:4940.
18. Arcari L, Limite LR, Adduci C, Sclafani M, Tini G, Palano F, Cosentino P, Cristiano E, Cacciotti L, Russo D, Rubattu S, Volpe M, Autore C, Musumeci MB, Francia P. Novel Imaging and Genetic Risk Markers in Takotsubo Syndrome. *Front Cardiovasc Med* 2021;**8**:703418.
19. Madias JE. Some thoughts about the different ballooning patterns in patients with recurrent takotsubo syndrome from the ones during their index takotsubo episode. *Am J Cardiol* 2019;**124**:319–321.