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EDITORIAL COMMENT
Heart failure

Takotsubo syndrome and chaos theory

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This editorial refers to 'Triptan-induced takotsubo syndrome: a case report' by T.J. Somers-Edgar et al., https://doi.org/10.1093/ehjcr/ytad221.

Can the flap of a wing cause a broken heart?

In 1961, mathematician and meteorologist Edward Norton Lorenz first noticed how complex and chaotic the prediction of specific atmospheric events could be, as minimal differences in baseline conditions may evolve into largely different outcomes. In 1963, he published a landmark study laying the foundation for what came to be called chaos theory.[1] Few years later, he described the butterfly effect: according to this theory, the main determinant of the final result (e.g. tornado in Texas) is not chaos but rather the interplay between the exact initial situation (predisposition) and the trigger (e.g. butterfly wings flap in Brazil).[2]

This model was found to be just as appealing for fields different from meteorology; for example, the heart rate can display a chaotic behaviour in response to emotional distress during psychotherapy.[3] Takotsubo syndrome (TTS) is an acute heart failure syndrome where a systolic dysfunction with a typical echocardiographic pattern develops in the absence of any culprit coronary artery disease and is usually followed by a recovery of the left ventricular ejection fraction within a few weeks or months. As the pathogenic pathways leading to a TTS attack are still not completely understood after more than three decades from the initial description,[4] the chaos theory model might find an application in this setting (*Figure 1*). Although several key features of this disease have been identified—including female preponderance,[5] association with a preceding emotional or physical stressor,[6] large burden of comorbidities,[7] and peculiar patterns of brain activation[8]—the occurring trigger might hesitate erratically into an acute TTS or, most of the time, into no acute cardiac abnormalities. In other words, from the same generic starting point (i.e. post-menopausal woman suffering emotional distress), minimal variations of the initial state and of the trigger could lead to different scenarios (*Figure 1*).

Triggers, clinical scenarios, and variegated outcomes of a heterogeneous syndrome

Takotsubo syndrome is a fairly variegated disease. Data from large registries depict a relatively heterogeneous population that could potentially involve men[5] and younger individuals.[9] Emotional triggers identify a subgroup of patients with excellent outcomes,[10] while physical triggers are associated with a worse prognosis, including higher rates of in-hospital complications and long-term mortality.[11] However, it remains unclear whether different triggers (i.e. emotional vs. physical) can lead to the activation of different pathologic pathways.[12] Of note, approximately one-third of the patients do not report any stressful trigger before the TTS onset.[13] Finally, a study applying cluster analysis to a cohort of patients with TTS identified four phenotypes with different clinical features and prognosis and with potentially different underlying pathophysiological processes.[14]

In the present issue of *European Heart Journal – Case Reports*, Somers-Edgar *et al.*[15] reported an interesting case of TTS, which occurred after the assumption of rizatriptan to treat migraine. This report depicts quite a 'classic' TTS phenotype: a woman affected by migraine who develops the syndrome without suffering any in-hospital complication. Accordingly, a nationwide study showed that TTS associated with migraine has a higher prevalence in the female sex and a better prognosis.[16]

The authors' hypothesis is that rizatriptan itself could have been the main trigger of the TTS attack in this case. In line with their hypothesis is the fact that triptans can be linked to TTS due to their coronary vasoconstrictor effect.[17] The patient reported having had similar but less intense chest pain episodes in the past after therapy with triptans, supporting the authors' view. Notwithstanding, it cannot be excluded that migraine itself could have exerted a causative role, either through pain (representing a physical trigger) or through associated brain functional abnormalities: it was shown that the amygdala displays structural plasticity and a correlation with headache frequency.[18] In TTS, the amygdala has been described as part of a network with altered connectivity in the acute phase.[19,20] Furthermore, it was shown that the activity of the amygdala is higher in those patients who will in the future develop TTS,[8] indicating a potential central role of this brain area in the pathogenesis of TTS. These neurologic connections might have had a crucial relevance in the present case.

In line with data available from the literature,[16] the patient had an excellent prognosis, showing a complete recovery at the follow-up visit on a low dose of beta blockers and angiotensin-converting enzymes.

Conclusion

This case report highlights the importance of recognizing TTS from the diagnostic, aetiological, pathophysiological, therapeutic, and

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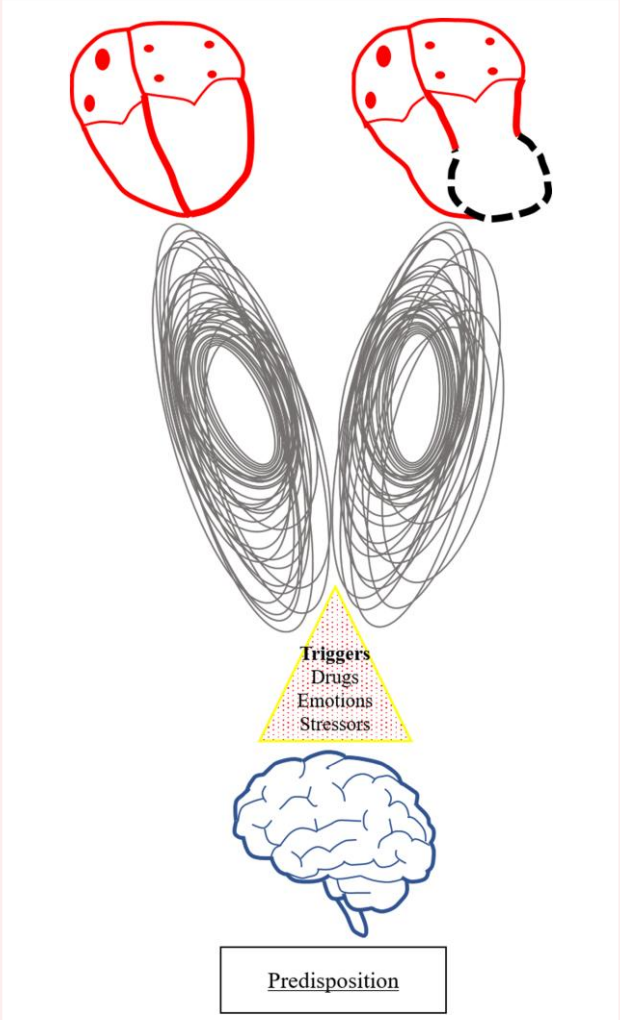

Figure 1 Graphical representation of chaos theory applied to Takotsubo syndrome. Triggers (butterfly wings flap) interact with an underlying vulnerable predisposing state potentially leading to acute Takotsubo syndrome. Small variations of these interactions and/or the initial state might lead to completely different pathways, graphically represented by different solutions in the Lorenz attractor, ending in opposite outcomes: no cardiac abnormalities or the typical Takotsubo syndrome manifestations.

prognostic points of view. Specific triggers might cause TTS in patients with an existing predisposition and should be avoided whenever possible. The lack of a complete understanding of the associations between triggers and TTS occurrence deems for extensive clinical and pre-clinical research, since the reason why a patient suffering long-standing migraine and chronically under triptan treatment should at once develop TTS remains unexplained. The understanding of the predisposing factor that increases the risk of TTS after a trigger might be useful in terms of screening and TTS prevention. The goal to pursue should be precision medicine, identifying different clusters of patients that share common features in order to tailor the management of each patient.

Lead author biography

Dr Vincenzo Nuzzi received his MD degree at the University of Rome 'La Sapienza', Italy. He then focused on clinical research in heart failure in Hull, UK, before starting his speciality training in cardiology at the University of Trieste. Part of his training was held in Cambridge (Royal Papworth Hospital, UK) and in Pisa (cardiac MR training, Italy). He is currently working as a cardiologist in the Heart Failure Unit of the Mediterranean Institute for Transplantations and Advanced Specialized Therapies (ISMETT, Palermo, Italy).

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Data availability

No new data were generated or analysed in support of this research.

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