Takotsubo Syndrome: A Complex and Varied Clinical Syndrome

Louise G. Shewan1,2, Michael Y. Henein3,4, Andrew J Stewart Coats1,2

1. Monash University, Australia
2. University of Warwick, Coventry, UK
3. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
4. Umeå Heart Centre, Umeå, Sweden

Corresponding author:
Professor Andrew J Stewart Coats, Academic Vice President, Monash University Australia and University of Warwick UK
E-mail: ajcoats@aol.com

Abstract

This special issue includes expert reviews and original research on Takotsubo syndrome (TTS) including the history of its identification and the unravelling of the pathophysiology of the different variants of the syndrome. The role of neurological stress or catecholaminergic overload are reviewed, as is the role of CNS disorders triggering TTS. Clinical presentation patterns of TTS and the most useful diagnostic tests are reviewed, including original research into a novel clinical score the ‘GET QT’ score to help in rapid differentiation of TTS from STEMI. There is also a review of TTS in the intensive care unit setting. The mechanisms of TTS including the role and assessment of the microcirculation in generating the classical myocardial dysfunction are reviewed in detail, as are the pathophysiological pathways of recurrent TTS. Lastly Singh, Akashi and Horowitz review the emerging treatment options for TTS. The issue also includes multiple elegant and fascinating case reports. TTS has come of age and now urgently needs adequate sized RCT’s.

Keywords: Takotsubo Cardiomyopathy; Review; Diagnosis; Acute Coronary Syndromes

Citation: Shewan LG, Henein MY and Coats AJS. Takotsubo Syndrome: A Complex and Varied Clinical Syndrome. International Cardiovascular Forum Journal. 2016;5:3-4. DOI: 10.17987/icfj.v5i0.348

This issue is a special issue that brings together experts to review and present original research into a still relatively newly described syndrome – Takotsubo syndrome (TTS). The history of this enigmatic syndrome is reviewed brilliantly by John Madias in the opening article. Nearly 3,000 papers are found in the quarter century since it was first described in Japanese in 1990, and most certainly there would be many more if we looked for all the different variants of the name of this syndrome. As is often the case there are clearly cases that we would now call TTS that were described before this date but which were not recognised as such at the time. In addition the role of neurological stress or catecholaminergic overload and their effects on the heart in a TTS like manner have been described many times before and after the date of the official birth of TTS as a diagnosis.

Two of the most authoritative authors on the interaction between the brain and the heart in TTS, Josef Finsterer and Claudia Stöllberger review the role of CNS disorders triggering TTS and provide compelling evidence for a similarity of cardiac effects between quite different disorders ranging from subarachnoid haemorrhage, through stroke to epilepsy, even encountering rare cases secondary to encephalitis, cerebral tumours and multiple sclerosis. They conclude that TTS can be triggered by any physical or psychogenic stress resulting in excessive levels of catecholamines, and importantly that patients exposed to severe stress from CNS diseases are potential candidates for developing TTS. They stress that CNS disease patients experiencing subarachnoid bleeding, seizures, ischemic stroke, or intra-cerebral bleeding are particularly prone to develop TTS and that as a result these patients should routinely undergo echocardiography if cardiac symptoms develop, if there are ECG changes, or if there are elevated biomarkers of myocardial infarction. CNS-triggered TTS they conclude needs to be more regularly and rapidly recognised since early treatment may improve outcomes in at risk patients. Hannah Masoud takes the CNS-Cardiovascular interaction further reviewing the links between psychiatric illness and TTS. High-risk patients can be triggered into a TTS episode by emotional or physical stress. She suggests increased use of echocardiography in acute medical units to detect potential TTS patients, who might otherwise be missed. She warns that influence of psychiatric illness on the pathogenesis of TTS may still be significantly underestimated, perhaps compounded by increasing specialisation in modern medical care.

Another leading expert Stefan Peters stresses the variability in clinical presentation patterns of TTS despite similar pathophysiological pathways, and Jen Li Looi and Andrew J Kerr review the clinical characteristics of a variety of TTS sub-types, also reviewing the various diagnostic modalities that may need to be used in different clinical settings. Loris Roncon and Marco Zuin evaluate the need for and value from serial measurements of ECG to pick up the classic evolving pattern of TS cardiac stress.

Vaidya and colleagues present original research evaluating the diagnostic utility in risk stratification of a score of simple clinical

* Corresponding author. E-mail: ajcoats@aol.com

ISSN: 2410-2636 © Barcaray Publishing
characteristics, the ‘GET QT’ score to help in rapid differentiation of TTS from STEMI. They found that 5 predictors were significant on multiple regression, female gender, LVEF, peak Troponin T, QTc interval and time to peak troponin T. The presence of 3 or more predictors had a sensitivity of 88.8%, specificity of 95.1% and negative predictive value of 90.9% to diagnose TTS. They suggest that the presence of 3 or more factors is highly specific to diagnose TTS, although this will clearly require larger scale independent studies for validation. Hannah Masoud also considers the special case of TTS in the intensive care unit where cases are both much more likely to occur but also paradoxically are also much more likely to be missed as the staff concentrate on other major organ disorders and miss the classical hallmarks of TTS. Of course in this setting catecholamine excess, the most likely trigger of TTS, is almost universal at some point in the clinical journey of these patients.

We then turn our attention to a more detailed understanding of the mechanisms of TTS and Nauman Khalid reviews the role of the microcirculation in generating the myocardial dysfunction of TTS. He concludes that the transient myocardial dysfunction of TTS is due to the combined effects of multivessel coronary vascular spasm, microvascular dysfunction, and neurogenic and catecholaminergic stunning of the myocardium, but also stressing that microcirculatory dysfunction may play a key role especially in the acute phases of the illness. Gowdar and Chhabra of Hartford review in detail the methods available to evaluate microvascular dysfunction in the setting of TTS, including invasive and non-invasive techniques. They evaluate the role of PET and magnetic resonance contrast along with novel Doppler echocardiographic methods. They also review the published studies of invasive microvascular function tests in TTS, including TIMI Frame Count, TIMI myocardial perfusion grade and intracoronary Doppler including provocative vasomotor studies to measure minimal microvascular resistance.

Kato, Kitahara and Kobayashi review recurrent TTS a fascinating clinical picture that may hold the key to more accurate definition of the pathophysiological pathways of this syndrome. They find that recurrence rates are reported up to 10% although mostly in the range of 1-2%, with a lower rate of multiple recurrences. They review the clinical features of recurrent TTS including increased susceptibility to stress, female gender and younger age. The morphological pattern of recurrent TTS appears to be distinctive with usually the same ballooning pattern in the recurrent event as in the index presentation although case reports of different ballooning patterns do exist, suggesting dynamic variations in the sensitivity of the cardiac adrenergic receptors may be responsible for different morphologic patterns. They also review preventive therapy for recurrent TTS and although β-blockers are intuitively the most logical two meta-analyses failed to show benefit of β-blockers for preventing recurrence, so treatment remains largely empirical. Singh, Akashi and Horowitz review the overall treatment options for TTS including the need for therapy in the acute phase, in convalescence and to prevent recurrence. Acute episodes of TTS can be complicated by hypotension, shock, cardiac arrhythmias, thromboembolic complications and heart failure, all of which should be treated on their own merits, as little evidence is available to suggest a different approach because of the TTS basis. In TTS thrombus formation in particular can occur in both right and left ventricular apices in 2 to 4% of cases, and they suggest that patients at higher risk such as those with extensive apical dyskinesia should be treated with unfractionated or low molecular weight heparin for the first 48 to 72 hours to reduce the risk of LV thrombus. For prevention of recurrences they conclude, as did Kato, that β-blockers neither modify the initial nor recurrent episodes of TTS whereas ACE inhibitors might help in TTS recovery and in reducing recurrence. In systematic reviews of observational series no correlation between the use of β-blocker therapy and rate of recurrence has been found, whereas there was a negative correlation between the ACE inhibitor use and the incidence of recurrence. As there may be confounders based on physicians’ choices between these various agents there is a clear need for randomized studies in TTS. In the recovery phase of TTS Singh and colleagues conclude there is no adequate evidence base for chronic therapy and surmise that although β-blocker therapy is regularly prescribed, the initial evidence shows a lack of efficacy of β-blocker therapy to improve survival. They suggest two possible explanations, the involvement of β2 rather than β1-adrenoceptor receptors or the use of inadequate β-blocker doses being usually used. They conclude with an assessment of possible future directions for intervention, including treatments targeting alterations in myocardial energy metabolism including modulating free fatty acids availability and efficient glucose utilisation. They hypothesize that the historical glucose, insulin, and potassium (GIK) regimen, which has shown mixed results in ischemia trials, could be a more logical strategy in TTS. Other metabolic agents such as trimetazidine and ranolazine that partially inhibit fatty acid oxidation and augment glucose utilization could also be promising acutely, as could perhexiline another older agent. Yet again we bemoan the lack of adequate RCT’s in TTS.

The issue finishes with some elegant and fascinating case reports and series in the form of well-illustrated letters to the editor. We welcome the reader to this issue. We believe TTS has come of age and urgently requires co-operatives to form to produce the needed RCT’s, to establish what is causing this syndrome and what treatments may help acutely, in the recovery phase and longer term.

Declarations of Interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the requirements for ethical publishing in biomedical journals.1

References
DOI: 10.17987/icfj.v2i1.4