Canadian Journal of Cardiology 36 (2020) 802–804

Editorial

Cardiogenic Shock With Takotsubo Syndrome vs Myocardial Infarction: Better Short-term Outcomes but Significant Long-term Risk and Need for Surveillance

Haran Yogasundaram, MD,[a,b] Anish Nikhanj, BSc,[a,b] and Gavin Y. Oudit, MD, PhD, FRCPC[a,b,c]

[a] *Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

[b] *Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada*

[c] *Department of Physiology, University of Alberta, Edmonton, Alberta, Canada*

See article by Sattler et al, pages 860-867 of this issue.

Cardiogenic shock (CS) can be defined as a "cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion" and is characterized by persistent hypotension, low cardiac index, and adequate or elevated filling pressures.[1-3] CS most commonly occurs in the setting of acute myocardial infarction (MI), but can arise from a number of etiologies including acute perimyocarditis, takotsubo cardiomyopathy (TTC), and hypertrophic cardiomyopathy.[3] In an observational study, acute MI comprised 68% of CS presentations, whereas 2% were secondary to TTC.[4] Of note, CS complicates approximately 5%-8% of presentations with ST-elevation myocardial infarction, 2.5% of non–ST-elevation myocardial infarction, and 4%-12% of TTC.[3,5,6] Universally, CS is associated with a worse prognosis.[1,7] As outcome data directly comparing patients with CS secondary to MI or TTC are limited, there is uncertainty about differences between short- and long-term outcomes in these populations. In the present issue of the *Canadian Journal of Cardiology*, Sattler et al. describe a mixed retrospective and prospective study with short- and long-term follow-up to evaluate outcomes in CS with MI or TTC.[8] Their findings may have important prognostic and management implications for patients presenting with CS.

Study to Evaluate Outcomes in CS in Takotsubo Syndrome and MI

The article by Sattler et al. describes a mixed retrospective and prospective, single-centre study to examine outcomes in patients with CS due to acute MI or TTC. Five hundred and thirty-two consecutive patients with CS and acute MI were retrospectively included in the study, whereas 138 consecutive patients with CS and TTC were enrolled prospectively. Patients were enrolled based on ESC criteria for the diagnosis of MI[9,10] and TTC;[11] 2 independent cardiologists verified the diagnosis of TTC. Fifty percent of patients with MI presented with ST-elevation. Patients were managed with guideline-directed therapy.[9-11] The primary outcome was all-cause mortality, whereas the secondary endpoint was a composite of all-cause mortality, stroke, malignant arrhythmia, heart failure, thromboembolic event, or recurrence of MI or takotsubo syndrome (TTS). The study sought to assess for any long-term differences in mortality in patients with CS between MI and TTS.

The mean age of the TTS and MI cohorts was 65 and 73 years, respectively. Seventy-six percent of the TTS cohort was female, compared with only 42% of the MI cohort, a difference that was statistically significant and likely reflects a well-described female preponderance for TTS.[12] Medical history, symptoms, clinical parameters, and laboratory values were similar across both cohorts, save for increased proportion of patients with a history of coronary artery disease, increased proportion of ST-segment elevation, and decreased proportion of T-wave inversion in the MI cohort relative to the TTS cohort, along with increased creatine phosphokinase levels. Left-ventricular ejection fraction was not significantly different at baseline between cohorts but was significantly reduced in the MI cohort at follow-up (33 ± 17% vs 45 ± 17%), a finding congruent with the literature.[13] The proportion of patients who developed shock, 18% of patients with TTS vs 12% of the MI cohort, were similar. Compared with the literature, the incidence of CS in TTS is slightly greater than previously reported incidences, which are between 5% and 12%.[6,7,14–16] In the present study, male patients with TTS were more likely than females to develop CS; this difference was not noted in the International Takotsubo Registry although the Registry did confirm higher mortality in patients with TTS and CS vs those without CS.[14] The mean follow-up duration was 947 days in the TTS cohort

Received for publication October 23, 2019. Accepted October 29, 2019.

Corresponding author: Dr Gavin Y. Oudit, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta T6G 2S2, Canada. Tel.: +1-780-407-8569; fax: +1-780-407-6452.

E-mail: gavin.oudit@ualberta.ca

See page 804 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.10.034

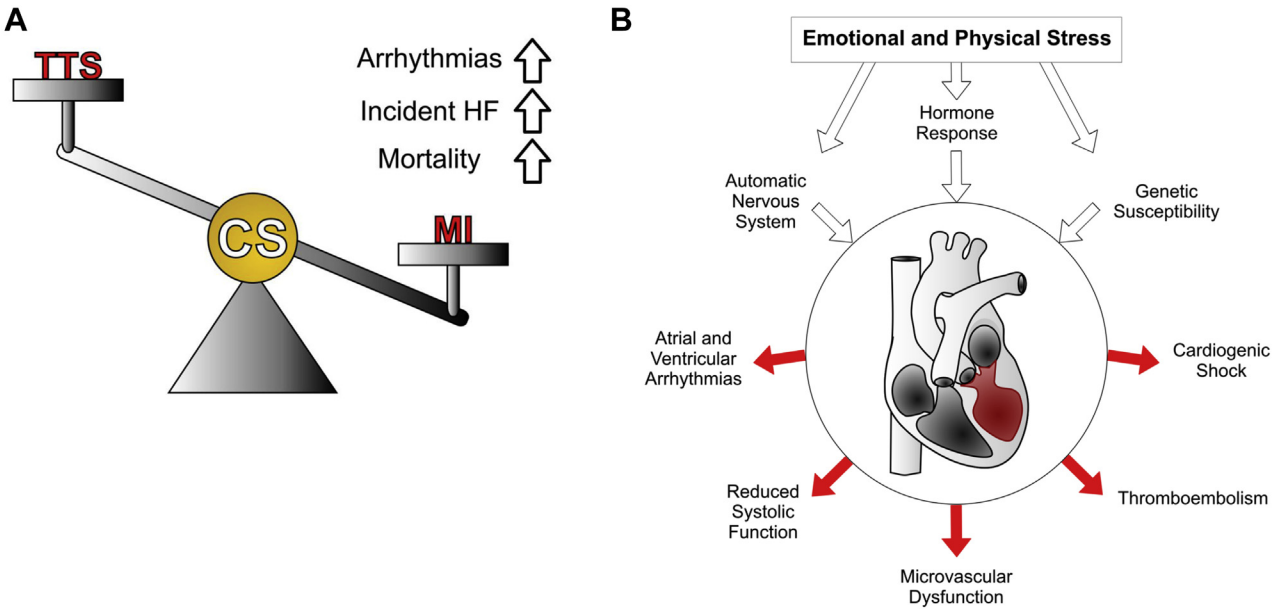

Figure 1. Comparison of the risk of adverse cardiac events in patients with takotsubo syndrome vs those with myocardial infraction in the setting of cardiogenic shock (**A**) and factors associated with takotsubo syndrome leading to adverse cardiac events (**B**). CS, cardiogenic shock; HF, heart failure; MI, myocardial infarction; TTS, takotsubo syndrome.

and 326 days in the MI cohort; the difference was primarily driven by increased early mortality in the MI cohort.

Patients with MI and CS had worse 30-day and overall outcomes than those with TTS and CS. The MI and CS cohort had significantly increased need for resuscitation (80% vs 24%), malignant arrhythmias (74% vs 28%), and mortality (71% vs 24%) within the first 30 days. The TTS and CS cohort in the present study had a greater incidence of life-threatening arrhythmias than previously reported (28% vs 11.4%).[17] During overall follow-up, 52% of the patients with TTS and CS had died compared with 76% of those with MI and CS, whereas the incidence of heart failure was 4% and 32%, respectively. Prior registry data not stratified by the presence of CS suggested similar short- and long-term mortality data in TTS and MI, suggesting that the worse outcomes in patients with MI in the present study are associated with the high-risk population identified by the presence of CS.[18] Importantly, the Kaplan-Meier analysis of the data demonstrated ongoing elevated risk of mortality in the TTS and CS cohort beyond the initial 30 days, driven by both cardiovascular and noncardiovascular causes. Interestingly, thromboembolic events were greater in the TTS and CS cohort vs the MI and CS cohort, which has been previously reported.[17]

Strengths and Weaknesses of the Sattler Study

The long-term evaluation of outcomes with CS in TTS vs MI is a major strength of this study; prior studies have evaluated TTS vs MI without stratifying patients with or without CS, used registry data, or did not have long-term outcomes. As TTS is becoming increasingly recognized in various contexts, there is significant relevance of this study to clinical practice.[12,19] There are some methodological weaknesses in the present study. The sample size is reasonable for a relatively uncommon condition as TTS but does limit interpretation of subgroup analyses. A potential source of bias is the lack of blinding of diagnosing cardiologists. However, the long-term follow-up and the inclusion of hard outcomes may mitigate this risk. Data in the MI cohort were collected retrospectively, whereas data in the TTS cohort were collected prospectively.

The finding that CS associated with TTS has lower short-term and overall mortality relative to CS associated with MI is a significant finding and is consistent with the literature.[18,20] However, the persistent elevation of mortality risk beyond the initial 30 days in the TTS and CS cohort suggests that TTS is not as benign as once postulated; these patients may benefit from long-term follow-up rather than only receiving acute cardiac care. The interesting finding that patients with TTS have greater rates of venous thromboembolism is also supported by the literature but is, currently, of unclear significance.[13,21] Indeed, the incidence of left-ventricular thrombus and cerebrovascular events is increased in patients with TTS, suggesting that a hypercoagulable state may be present in these patients.[21] Randomized controlled trials are needed to determine the best management strategy for patients with TTS and CS to reduce long-term mortality. Considerations such as screening for malignancy, as well as medical therapy with beta-blockade, angiotensin converting enzyme inhibition/angiotensin receptor blockade, and antithrombotic therapy, should be evaluated.[13,22]

Conclusions

Cardiogenic shock in the setting of MI or TTC is associated with high mortality. Based on the results of the study by Sattler et al., patients with CS due to MI have increased malignant arrhythmias, incident heart failure, and mortality compared with TTC, and, therefore, MI should be recognized as implying a worse prognosis in CS (Fig. 1A). Importantly,

this difference narrowed over long-term follow-up, suggesting that patients with TTS retain a persistent state of susceptibility to cardiac dysfunction and adverse events (Fig. 1B). Further research is required to elucidate pathophysiological mechanisms to explain the persistently high mortality in TTC after the acute period and the best management strategies for these patients.

Funding Sources

The authors have no relevant funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017;136:e232-68.
2. Bellumkonda L, Gul B, Masri SC. Evolving concepts in diagnosis and management of cardiogenic shock. Am J Cardiol 2018;122:1104-10.
3. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation 2008;117:686-97.
4. Harjola VP, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015;17:501-9.
5. Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 2006;27:1523-9.
6. Stiermaier T, Eitel C, Desch S, et al. Incidence, determinants and prognostic relevance of cardiogenic shock in patients with takotsubo cardiomyopathy. Eur Heart J Acute Cardiovasc Care 2016;5:489-96.
7. Almendro-Delia M, Núñez-Gil IJ, Lobo M, et al. Short- and long-term prognostic relevance of cardiogenic shock in takotsubo syndrome: results from the RETAKO registry. JACC Heart Fail 2018;6:928-36.
8. Sattler K, El-Battrawy I, Gietzen T, et al. Improved outcome of cardiogenic shock triggered by takotsubo syndrome compared to myocardial infarction. Canadian J Cardiol 2020;36:860-7.
9. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017;39:119-77.
10. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
11. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016;18:8-27.
12. Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of takotsubo cardiomyopathy in the United States. Am Heart J 2012;164:66-71.e61.
13. Han PL, Yang ZG, Diao KY, et al. Comparison of clinical profiles between takotsubo syndrome and acute coronary syndrome: a systematic review and meta-analysis. Heart Fail Rev 2019. https://doi.org/10.1007/s10741-019-09846-6.
14. Di Vece D, Citro R, Cammann VL, et al. Outcomes associated with cardiogenic shock in takotsubo syndrome. Circulation 2019;139:413-5.
15. Looi JL, Lee M, Webster MWI, To ACY, Kerr AJ. Postdischarge outcome after takotsubo syndrome compared with patients post-ACS and those without prior CVD: ANZACS-QI 19. Open Heart 2018;5:e000918.
16. Schneider B, Athanasiadis A, Schwab J, et al. Complications in the clinical course of tako-tsubo cardiomyopathy. Int JCardiol 2014;176:199-205.
17. El-Battrawy I, Lang S, Ansari U, et al. Prevalence of malignant arrhythmia and sudden cardiac death in takotsubo syndrome and its management. Europace 2018;20:843-50.
18. Redfors B, Vedad R, Angeras O, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction—a report from the SWEDEHEART registry. Int J Cardiol 2015;185:282-9.
19. Madias JE. Myocardial infarction with nonobstructive coronary artery disease in patients younger than 55 years old: how many of them had takotsubo syndrome? Can J Cardiol 2018;34:1089.e1013.
20. Vallabhajosyula S, Dunlay SM, Murphree DH Jr, et al. Cardiogenic shock in takotsubo cardiomyopathy versus acute myocardial infarction: an 8-year national perspective on clinical characteristics, management, and outcomes. JACC Heart Fail 2019;7:469-76.
21. Baldetti L, Pagnesi M, Gallone G, et al. Thrombotic complications and cerebrovascular events in takotsubo syndrome: a systematic review and meta-analysis. Can J Cardiol 2019;35:230.e239-230.e210.
22. Ghadri JR, Kato K, Cammann VL, et al. Long-term prognosis of patients with takotsubo syndrome. J Am Coll Cardiol 2018;72:874-82.