

Perioperative Takotsubo Cardiomyopathy: a Review Article

Varisara Charoenyingpaisal, Nalin Chokengarmwong

King Chulalongkorn Memorial Hospital, Thai Red Cross Society and Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Abstract

Perioperative Takotsubo cardiomyopathy, acute transient left ventricular dysfunction without significant coronary artery obstruction, can occur during intraoperative period and within 30-days postoperative period. It is found to be more common and more fatal than non-perioperative type. Neither the understanding of clear pathogenesis nor tools to predict the occurrence and recurrence, it is reasonable to diminish any possible triggers such as patient's anxiety, light anesthesia, inadequate pain control

and residual paralysis. In patients with history of Takotsubo cardiomyopathy, the operation should be performed with available intensive care unit and percutaneous coronary intervention. A multidisciplinary team approach is needed. The assessment of the echocardiogram and complications must be noted. The supportive management to preserve organ perfusion is still the mainstream of management while the inotrope and intra-aortic balloon pump must be cautious.

Keywords: stress-induced cardiomyopathy, Takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy (TCM) is acute transient left ventricular dysfunction which is not the result of obstructive coronary artery disease. It can be triggered by emotional stress, physical stress, or unknown cause. The recovery of left ventricular dysfunction is usually within 4-8 weeks.¹ 'Takotsubo' is derived from Japanese word which means 'Octopus trap' because it resembles left ventricular appearance at

the end of systole in the early reported cases of Takotsubo cardiomyopathy. TCM also goes by many names such as stress-induced cardiomyopathy, broken heart syndrome, and apical ballooning syndrome.¹ Perioperative takotsubo cardiomyopathy (pTCM) is secondary subtype of European Society of Cardiology classification which anesthesia may have been one of contributing factor.² The diagnosis of pTCM occurred during intervention, surgical, or anesthetic procedure or within 30-days postoperative period.³

TCM was first described in 1983 at Hiroshima City Hospital.² The first diagnostic criteria were published in 2003 as Mayo clinic diagnostic criteria which was the most well-known and referred criteria.⁴ In 2006, TCM was classified as a primary acquired cardiomyopathy by American College of Cardiology and American Heart Association. The worldwide awareness of TCM was raised. There are many institutes which published their own diagnostic criteria such as Japanese guideline⁵, Johns Hopkins criteria⁶, Gothenburg criteria.⁷ Lately in 2015, European Society of Cardiology published 'International expert consensus document of Takotsubo cardiomyopathy' with the International Takotsubo Diagnostic Criteria.^{1,8} (Table 1) It was found that concomitant significant coronary artery disease is about 10-29% but the obstructive lesion is not related to the regional wall motion abnormality that happened.⁸

Incidence and mortality rate

Among the patients presenting with acute coronary syndrome were found to be TCM 1-2%.^{3,9} The incidence is 2-9/100,000 persons annually. But it is higher in pTCM which is 1/6,700 persons.^{2,10} TCM is found mostly in women (89.8%) with mean age of 66.8 years old. In the perioperative setting, it is also female predominant (80%) but higher proportion of male patients with lower mean age at 54 years old. However, TCM is still under detection, especially in the setting without percutaneous coronary intervention center. In perioperative setting, the mortality rate (6.1% vs 4.1-4.5%) and the recurrence rate (11.0% vs 1.2%) are higher than

non-perioperative setting.² In contrast, the mean left ventricular ejection fraction (LVEF) is worse than the non-perioperative setting (35% vs 42%).³

Etiology

The pathogenesis is still unclear but may be multifactorial. It was believed to be about cardio-neurological organ crosstalk or 'Brain-Heart interaction'.¹¹ When there is a stress stimuli, the cytokines are released and increased sympathetic stimulation to limbic system which will generate impulse to activate autonomic nervous system in medullary center to potentiate norepinephrine releasing from pre and post synaptic neurons and stimulus adrenal medulla to potentiate epinephrine releasing from cardiac and extracardiac sympathetic nerves. Catecholamine surge will occur and activate adrenergic receptor at heart causing direct and indirect injury.

The indirect injury is likely to be coronary artery spasm and microvascular dysfunction.¹² As direct injury, excessive catecholamine will cause calcium overload at sarcoplasmic reticulum via cAMP pathway and result in excessive contraction. Contraction band necrosis was found as pathologic finding. The supraphysiologic level of epinephrine will cause molecular switch of β -2 adrenergic receptor at myocardium and result in negative inotropic response. The β -2 adrenergic receptors densely locate at the apex with the nature of apical-basal gradient.¹³ That explains clinical finding of apical ballooning. The hypercontractility happens at the base because it has the most innervation of sympathetic nerves. There is also atypical type of TCM which is not

Table 1 International Takotsubo Diagnostic Criteria (InterTAK diagnostic criteria)

1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) pre-senting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion ab-normality is present in the subtended myocardial territory of a single coronary artery (focal TTS).
2. An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (e.g. subarachnoid hemorrhage, stroke/transient ischemic attack, or sei-zure) as well as pheochromocytoma may serve as triggers of Takotsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in Takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.
8. Postmenopausal women are predominantly affected.

presenting as apical ballooning. The fact that the individual receptor distribution can vary was claimed as the explanation. However, there was a case report of the patient with recurrent TCM with new pattern of regional wall motion abnormality.¹⁴ This makes the etiology still be unexplainable.

Recently, TCM was found to be accompanied by myocardial and systemic inflammation which persisted for more than 5 months. Scally and colleagues found evidence of macrophage mediated myocardial inflammation of patients with acute TCM with increased systemic inflammatory cytokines such as IL-6 and white blood cell count.¹⁵ It is suspicious whether the recovery of LVEF found in TCM is the exact resolution of this cardiomyopathy or it is a spectrum of long-term heart failure phenotype. Further study is needed to answer whether these myocardial

and systemic inflammations can be used as therapeutic targets in the future.

Predisposing factors

Hormonal factor: TCM is predominantly found in postmenopausal women.¹⁶ Estrogen declination may be the factor. Estrogen has vasomotor effect via up-regulation of endothelial nitric oxide synthase which decreases sympathetic response due to mental stress and attenuates catecholamine mediated vasoconstriction. However, there is lack of clinical trial or evidence base for a role of estrogen replacement therapy.¹⁷

Genetic factor: The increasing of adrenergic polymorphism and GRK5 gene activity was found in some studies.¹⁸ Borchert et al. created 'Takotsubo in dish' model by creating inducible pluripotent stem cell cardio-

myocyte derived from somatic cells of TCM patients. The study found an overactivity β -adrenergic pathway and increased sensitivity to catecholamine in Takotsubo specific induced pluripotent stem cell cardiomyocyte.¹⁹

Neurological factor: This relates to the brain-heart interaction called neurogenic stunned myocardium dysfunction. It was also associated with aneurysmal subarachnoid hemorrhage, seizure and stroke.²

Psychological factor: There is the systematic review from 19 meta-analysis studied in 1,109 TCM patients by Pelliccia and coworkers called 'COUNTS' study reported the comorbidities associated with TCM.²⁰ The result was not different from which associated with acute coronary syndrome except the higher percentage of psychologic disorder. The psychological disorder was found in 24% among these patients. Most are anxiety disorders. Some medications for psychologic disorder, such as serotonin-norepinephrine reuptake inhibitors, may alter the catecholamine level but there has been no study about this correlation.¹

Clinical presentation

The signs and symptoms of TCM are indistinguishable from acute myocardial infarction. In awake patients, pTCM are more frequently complain of dyspnea (44%)² compare to non-perioperative setting which is mostly complain of chest pain (70%).^{1,9} In perioperative setting, it is more likely to present with evidence of heart failure (57-66%), arrhythmia (36%) and cardiac arrest (30%).^{2,3} The ECG finding is mostly

ST-elevation (44%)⁹ in both settings but in perioperative setting there will be more presenting with ST-depression (32%) comparing to non-perioperative setting (8%).² The cardiac biomarker is found modest elevation of troponin but significant elevation of brain natriuretic peptide (BNP). The high BNP: troponin ratio is the same in both setting.²

The coronary angiography will find insignificant coronary occlusion which is not related to regional wall motion abnormality. The left ventriculogram may present the apical ballooning with narrow base in the typical type. The echocardiogram is the important noninvasive imaging modality to show the evidence of left ventricular myocardial dysfunction as wall motion abnormality which is usually not related to single coronary artery territory.²¹ The wall motion index $\geq 1.75\%$ for >4 dysfunctional segments is associated to TCM with 80% sensitivity, 100% specificity.⁸ The echocardiogram will provide LVEF and the evaluation of the complications which are left ventricular outflow tract obstruction, mitral regurgitation, intraventricular thrombus. The picture of coronary angiogram and echocardiogram of the patient with perioperative Takotsubo cardiomyopathy is shown in Figure 1. The patient developed Takotsubo cardiomyopathy presenting with cardiogenic shock after explore laparotomy with bowel resection. The echocardiogram showed the reduced ejection fraction with apical wall akinesia. With the history of single vessel disease with previous percutaneous coronary intervention, the coronary angiogram was unremarkable. There was no in-stent

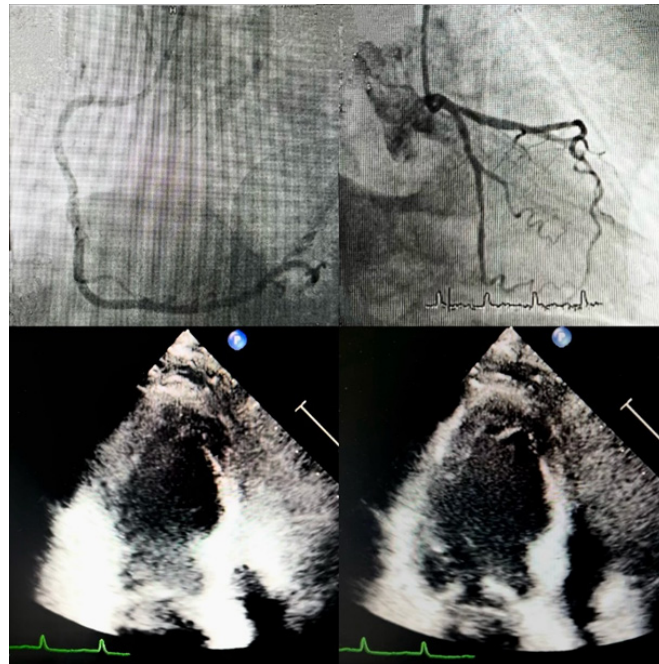


Figure 1 Coronary angiogram and echocardiogram of patient with perioperative Takotsubo cardiomyopathy

restenosis. Since TCM is hardly distinguished from acute myocardial infarction, InterTakotsubo Registry recommended the use of InterTAK diagnostic score if the score >70 points indicate high probability for the presence of TCM.⁸ (Table 2)

Table 2 InterTAK diagnostic score

	Points
Female	25
Emotional stress	24
Physical stress	13
No ST-segment depression	12
Psychiatric disorder	11
Neurologic disorder	9
QTc prolongation	6

Timing of presentation

The event mostly happened in the postoperative phase. In the study of 21 patients diagnosed with pTCM, it was found that intraoperative TCM occurred in 29% of patients, 33% happened within 3 days postoperatively, 14% happened in postoperative day 3 to day 7 and the rest (24%) happened beyond postoperative day 7.³

Types of Takotsubo cardiomyopathy

The types of TCM were classified by the pattern of the regional wall motion abnormality. In the study of 131 perioperative patients, the data showed that 68% presented a classical

apical ballooning pattern.² The incidence of this apical ballooning pattern was lower than the non-perioperative setting (81.7%).¹⁸ There were also presenting with atypical patterns which were midventricular (10%), basal (8%), and global akinesia (4%). A focal type presentation was also reported.³ In an observational study, atypical types were associated with lower age group, neurological condition, more frequent ST-depression ECG presentation and lower LVEF compared to typical type.²² (Table 3)

Perioperative Takotsubo cardiomyopathy

Anesthesiologists may encounter pTCM in many situations. It can occur in patients undergoing either surgical procedure or diagnostic procedure. It can happen in the critically ill patients, in patients with pheochromocytoma, acute central nervous system condition and even

with allergic reaction.² The most reported choice of anesthesia related to pTCM occurrence is general anesthesia (66-76%).^{2,3} Locoregional anesthesia was reported 15% which is mostly spinal anesthesia (10%).² Most of cases were undergoing elective intervention (62%).³ The triggers during perioperative periods can be either physiological or emotional stressors such as patient's own anxiety, surgical stress, light anesthesia, inadequate pain control, hemodynamic instability, the administration of epinephrine or dobutamine, anaphylaxis or allergic reaction, fluid overload, and sepsis condition.^{2,16}

Patient with history of previous Takotsubo cardiomyopathy (Figure 2)

Preoperative management

There is inadequate data with evidence-based education for a tool to identify the patients

Table 3 Comparison between perioperative Takotsubo cardiomyopathy and non-perioperative Takotsubo cardiomyopathy

	Perioperative Takotsubo cardiomyopathy	Non-perioperative Takotsubo cardiomyopathy
Clinical presentation	More frequently present with dyspnea, heart failure, arrhythmia, cardiac arrest	Mostly chest pain
ECG finding	Mostly ST-elevation but more presenting with ST-depression	Mostly ST-elevation
Cardiac biomarker	Modest elevation of troponin but significant elevation of BNP, high BNP: troponin ratio	Same as perioperative setting
Pattern	Lower incidence of apical ballooning pattern, also present with atypical patterns	Mostly classical apical ballooning pattern

Patient with history of TCM

Goal: Minimize possible triggers, provide the lowest stimulation, monitor rigorously

Preoperative period

- Assess functional capacity, ECG, echocardiogram and any remaining complications from previous TCM
- Cardiologist consultation
- ICU and percutaneous coronary intervention availability
- Preoperative anxiety management: pharmacological approach (anxiolytic drugs), psychological approach (patient education and comfort)

Intraoperative period

Goal: Prevent light anesthesia, inadequate pain control, residual paralysis

- Monitoring with high level of vigilance
- Invasive monitoring, bispectral index, peripheral nerve stimulation, TEE should be considered individually.
- Choice of anesthesia is depended on patient's condition and surgical procedure.
- Regional anesthesia with appropriate sedation is recommended if possible.
- Anesthetic drugs with less potential of myocardial depression
- Smooth intubation and extubation

Postoperative period

- Fully reversal to avoid residual paralysis
- Adequate pain control
- Close monitoring in ICU

*Takotsubo cardiomyopathy (TCM), Electrocardiography (ECG), Intensive care unit (ICU), Transesophageal echocardiogram (TEE)

Figure 2 Perioperative management for patient with history of previous Takotsubo cardiomyopathy

at risk of recurrence. No anesthetic strategy can totally prevent the recurrence of TCM. The anesthetic goal is to minimize any possible triggers and provide the lowest stimulations with rigorous monitoring. The patients with the history should be operated on in the hospital with percutaneous coronary intervention center. Intensive care unit (ICU) for postoperative period should be available. The preoperative trigger is

mostly the anxiety of the patients to anticipate the surgery. There is a suggestion of preoperative anxiety management with not only pharmacological approach, anxiolytic drugs, but also psychological approach such as patient educations before patient's transfer to operative room.²³ The goal is patient's psychological comfort. The role of beta blockers in preoperative period is unclear.

Intraoperative management

Apart from ASA standard monitoring, there are suggestions of the invasive continuous blood pressure monitoring, 5-lead ECG, urine output, bispectral index, peripheral nerve stimulation and even transesophageal echocardiography.²³ However, the goal to prevent light anesthesia and inadequate pain control, and to avoid the residual of neuromuscular blockade are the integral principles for all anesthesiologists to provide to every patients whether having the history of TCM or not. But the important thing is the high level of vigilance since TCM is not clearly known about its real nature and pathogenesis. The recovery of LVEF may not mean the complete resolution of the cardiomyopathy.

The choice of anesthesia depends on the patient's conditions and surgical procedures. Regional anesthesia is considered as benefit for diminishing the stress response and being excellent postoperative analgesia without facing the stress from intubation and extubation. But the feeling of paralysis can be one of the trigger, so it is recommended to combine regional anesthesia with appropriate sedation.²³ General anesthesia has the benefit of the patient's unconsciousness, hemodynamic stability, and no limitation with any surgical procedures. The chosen anesthetic agents should have less potential for myocardial depression. The intubation and extubation should be brief and smooth. Maintaining hemodynamic stability, adequate depth of anesthesia and pain control and avoiding residual neuromuscular blockade should be provided.

Postoperative period

It is recommended to close monitor in ICU. Adequate postoperative pain control should be ensured.

Perioperative management with patient with active Takotsubo cardiomyopathy (Figure 3)

In the case of elective surgery, it should be postponed until the resolution of the wall motion abnormality.²⁴ In emergency surgical conditions, inform consent and communication with patient and surgeon should be done with risks-benefits discussion. Cardiologist consultation is needed. The evaluation should be focused on hemodynamic stability and complications. These can be left ventricular outflow tract obstruction (LVOTO), mitral regurgitation due to systolic anterior motion, arrhythmia, intraventricular thrombus with the potential of anticoagulant use. The patients were whether currently depended on vasopressor, inotrope and/or mechanical circulatory support, such as left ventricular assisted device (LVAD).²⁵ The ICU availability needs to be confirmed.

In the patient with anticipated pTCM, intraoperative transesophageal echocardiogram is recommended. Rigorous and invasive monitoring with a high level of vigilance should be provided. In the presence of dynamic LVOTO and/or mitral regurgitation due to SAM, adequate preload is needed together with avoiding tachycardia. Bradycardia is preferred. Afterload needs to be maintained. Inotropes and intra-aortic balloon pump (IABP) are contraindicated. The phenylephrine is recommended as vasopressor of choice

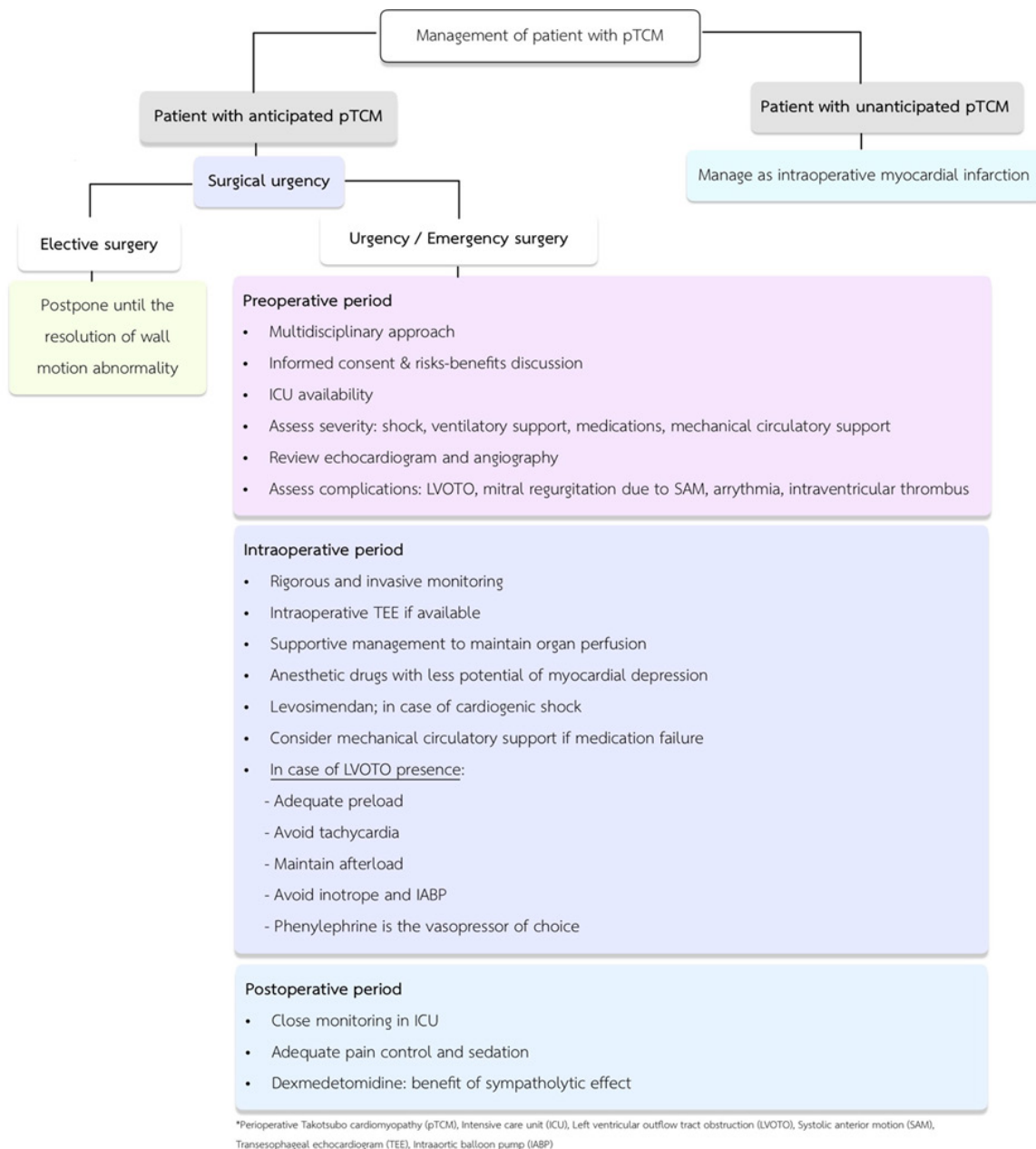


Figure 3 Perioperative management with patient with active Takotsubo cardiomyopathy

but be used with caution due to potential of causing coronary vasospasm.² If unanticipated pTCM occurs during the procedure, option of management is depended on the acuteness and timing. It is unable to distinguish pTCM from acute myocardial infarction. If the event occurs after anesthetic induction but before the start of

surgery which is not urgency or emergency. The operation should be postponed. The patient should be stabilized in ICU. Cardiologist consultation and cardiac catheterization should be done afterward.

If the event occurs in the middle of surgery, the goal is to maintain hemodynamics. The team

must be informed and discuss whether the surgery can be rapidly ended or deferred. Calling for help and cardiologist consultation are recommended. The defibrillator must be available inside the operating room. Adequate oxygenation, ventilation and hemodynamic stability need to be ensured. If unstable hemodynamic situation occurs, vasopressor and inotropic drugs should be promptly initiate for circulatory support. Mechanical circulatory support should be considered in case of medication failure. Early postoperative cardiac catheterization should be done to exclude acute coronary syndrome.²⁶

The role of inotropic drugs is widely criticized because catecholamine is noted to be the predictor of in-hospital death and to play as the major role of TCM's pathogenesis.⁹ Being the diagnosis of exclusion, pTCM is impossible to instantly identified as a cause of hemodynamic instability intraoperatively or to be distinguished from myocardial infarction. To achieve sustainable hemodynamics, vasopressors or inotropes may be needed along with investigation. It might be difficult to completely avoid using inotropic drugs or to mark them as contraindication in TCM. The recommendation is to use with great caution with the lowest dose as possible with the shortest duration. However, the use of mechanical circulatory support should be considered in case of no response to inotropes.³ It is recommended to use extracorporeal membrane oxygenation or temporary LVAD instead of IABP in the TCM patient with cardiogenic shock.²⁷ However, levosimendan, the calcium sensitizer and cAMP independent inotrope, is considered as inotrope

of choice in TCM with cardiogenic shock with the benefit of reversing negative inotropic effect without significant increasing intracellular calcium and cAMP.²⁸ It also provides cardioprotective property. There are studies found that levosimendan can rapidly restore left ventricular function in TCM but there is still low level of evidence.²⁹

The use of dexmedetomidine in TCM is also suggested.³⁰ Because of the centrally acting α -2 agonist effect, it is considered to have benefit from its sympatholytic effects. There is still no clinical trial available. The role of ACEi or ARB is considered to improve the 1-year survival but it is unable to prevent the recurrence.² The use of beta blocker is initiated to lower the heart rate and to ameliorate the intensity of autonomic sympathetic stimulation but there is still no evidence of any survival benefit and recurrence prevention.⁹

Summary

Takotsubo cardiomyopathy is a transient condition, but the outcome can be fatal especially in perioperative setting. There are many situations that anesthesiologists may encounter with pTCM as the numerous triggers contributed to the process of surgery. Without the criteria to predict the occurrence of pTCM, it is reasonable to diminish triggers or stress by providing patient's anxiety management, adequate depth of anesthesia and pain control with a high level of vigilance. However, there is still no prevention and no ideal anesthetic technique. The presentation of pTCM is undistinguished from the acute myocardial

infarction. The initial management of acute myocardial infarction should be done until it can be ruled out by coronary angiography. Supportive treatment to achieve sustainable hemodynamics is favorable. Avoiding catecholamines use is also recommended along with the encouragement of using mechanical circulatory support in patients with cardiogenic shock. Further study of the role of therapeutic targets on myocardial and systemic inflammations is needed.

What an anesthesiologist should know

- pTCM mostly occurs in the postoperative period.
- Treat as acute myocardial infarction until it can be ruled out.
- The recurrence of pTCM can occur. No proven strategy can fully prevent the recurrence.
- No available tool to identify patients at risk. High vigilance of monitoring and avoidance of triggers are recommended.
- There is no ideal anesthetic technique. A multidisciplinary team approach is needed.
- The decision to postpone the operation depends on the urgency of surgery. Risk-benefit discussion should be held with the patient and family.

References

1. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on Takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J*. 2018;39:2032-46.
2. Hessel EA, 2nd. Takotsubo cardiomyopathy and its relevance to anesthesiology: a narrative review. *Can J Anaesth*. 2016;63:1059-74.
3. Guzzo MEG, Novas DS, Iglesias FA, Bisurgi DD, Domenech G, Terrasa SA. Anesthetic implications of perioperative Takotsubo syndrome: a retrospective cohort study. *Can J Anaesth*. 2021;68:1747-55.
4. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol*. 2003;41:737-42.
5. Kawai S, Kitabatake A, Tomoike H. Guidelines for diagnosis of Takotsubo (apical) cardiomyopathy. *Circ J*. 2007;71:990-2.
6. Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? *Cell Mol Neurobiol*. 2012;32:847-57.
7. Schultz T, Shao Y, Redfors B, et al. Stress-induced cardiomyopathy in Sweden: evidence for different ethnic predisposition and altered cardio-circulatory status. *Cardiology*. 2012;122:180-6.
8. Ghadri J-R, Wittstein IS, Prasad A, et al. International expert consensus document on Takotsubo syndrome (Part II): diagnostic workup, outcome, and management. *Eur Heart J*. 2018;39:2047-62.
9. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373:929-38.
10. 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;164:215-21.
11. Hessel EAI. The brain and the heart. *Anesth Analg*. 2006;103:522-6.

12. Lüscher TF, Templin C. Is Takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. *Eur Heart J*. 2016;37:2816-20.
13. Paur H, Wright PT, Sikkil MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a β_2 -adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. *Circulation*. 2012;126:697-706.
14. Izumo M, Akashi YJ, Suzuki K, Omiya K, Miyake F, Ohtaki E. Recurrent Takotsubo cardiomyopathy with variant forms of left ventricular dysfunction. *J Cardiol Cases*. 2010;2:e37-40.
15. Scally C, Abbas H, Ahearn T, et al. Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy. *Circulation*. 2019;139:1581-92.
16. Assad J, Femia G, Pender P, Badie T, Rajaratnam R. Takotsubo syndrome: a review of presentation, diagnosis and management. *Clin Med Insights Cardiol*. 2022;16:11795468211065782.
17. 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.e1.
18. Spinelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimarco B. L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. *Eur J Heart Fail*. 2010;12:13-6.
19. Borchert T, Hübscher D, Guessoum CI, et al. Catecholamine-dependent β -adrenergic signaling in a pluripotent stem cell model of Takotsubo cardiomyopathy. *J Am Coll Cardiol*. 2017;70:975-91.
20. Pelliccia F, Parodi G, Greco C, et al. Comorbidities frequency in Takotsubo syndrome: an international collaborative systematic review including 1109 patients. *Am J Med*. 2015;128:654.e11-9.
21. Izumo M, Akashi YJ. Role of echocardiography for Takotsubo cardiomyopathy: clinical and prognostic implications. *Cardiovasc Diagn Ther*. 2018;8:90-100.
22. Ghadri JR, Cammann VL, Napp LC, et al. Differences in the clinical profile and outcomes of typical and atypical Takotsubo syndrome: data from the International Takotsubo Registry. *JAMA Cardiol*. 2016;1:335-40.
23. Agarwal S, Sanghvi C, Odo N, Castresana MR. Perioperative Takotsubo cardiomyopathy: implications for anesthesiologist. *Ann Card Anaesth*. 2019;22:309-15.
24. Muthachen NR, Sethuraman M. Anesthetic management of a patient with Takotsubo cardiomyopathy presenting for surgical clipping of intracranial aneurysm. *J Anaesthesiol Clin Pharmacol*. 2017;33:547-8.
25. Mohammedzein A, Taha A, Salwan A, Nambiar R. Impella use in cardiogenic shock due to Takotsubo cardiomyopathy with left ventricular outflow tract obstruction. *JACC: Case Reports*. 2019;1:161-5.
26. Ludbrook GL, Webb RK, Currie M, Watterson LM. Crisis management during anaesthesia: myocardial ischaemia and infarction. *Qual Saf Health Care*. 2005;14:e13.
27. 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.
28. Cholley B, Levy B, Fellahi JL, et al. Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper. *Crit Care*. 2019;23:385.
29. Mukhtar A, Moharam H, Sarhan K, Hosni H, Salah M. Liver transplantation using dexmedetomidine in a patient with a history of Takotsubo cardiomyopathy. *A A Case Rep*. 2016;6:14-6.
30. Wang K, Wu M, Xu J, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. *Br J Anaesth*. 2019;123:777-94.