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REVIEW ARTICLE/BRIEF REVIEW

Takotsubo cardiomyopathy and its relevance to anesthesiology: a narrative review

La cardiomyopathie de Tako-Tsubo et sa pertinence pour l'anesthésiologie: un compte-rendu narratif

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Abstract

Purpose *Takotsubo cardiomyopathy (TTCM) is a form of stress cardiomyopathy that may occur in the perioperative period and among the critically ill. Therefore, anesthesiologists should be aware of its diagnosis and treatment. The aim of this narrative review is describe the features of TTCM and its relevance to the practice of anesthesiology.*

Principal findings *Takotsubo cardiomyopathy occurs in about 2-9/100,000 persons in the general population annually and may occur in up to one in 6,700 cases in the perioperative period. Takotsubo cardiomyopathy often presents like an acute coronary syndrome and is likely caused by excessive catecholamine stimulation. Although its early course may be complicated, more than 90% of patients survive the acute episode. A review of the literature revealed 131 cases encountered in many different types of surgical procedures, with 37% occurring during anesthesia or surgery and 58% occurring postoperatively. Compared with non-perioperative cases, this population involved more males, was younger, less likely to have an obvious precipitating factor, less likely to present with chest pain, and less likely to exclusively exhibit the apical ballooning pattern. In addition, perioperative TTCM had a lower ejection fraction and was prone to higher mortality. Detection is facilitated by early echocardiography. Anesthesiologists may encounter TTCM in other situations including patients undergoing other non-surgical procedures (e.g., electroconvulsive therapy), those with acute central nervous system conditions, those with pheochromocytoma, in other critical illnesses, and during allergic reactions.*

Conclusion *Perioperative TTCM is more common than appreciated and should be considered in any hospitalized patient presenting with acute coronary syndrome and/or hemodynamic instability, acute respiratory distress, as well as cardiac arrhythmias and arrest.*

Résumé

Objectif *La cardiomyopathie de Tako-Tsubo (CMTT) est une forme de cardiomyopathie de stress qui peut survenir en période périopératoire et chez les patients gravement malades, c'est pourquoi les anesthésiologistes devraient être au fait de son diagnostic et de son traitement. L'objectif de ce compte-rendu narratif est de décrire les caractéristiques de la CMTT et sa pertinence à la pratique de l'anesthésiologie.*

Constatations principales *La cardiomyopathie de Tako-Tsubo survient chaque année chez approximativement 2-9/100 000 personnes dans la population générale et peut survenir jusqu'à un cas sur 6700 en période périopératoire. La cardiomyopathie de Tako-Tsubo se présente souvent sous forme d'un syndrome coronarien aigu et est probablement provoquée par une stimulation excessive de la catécholamine. Bien que son décours précoce soit compliqué, plus de 90 % des patients survivent à l'épisode aigu. Un compte-rendu de la littérature a dénombré 113 cas rencontrés dans divers types d'interventions chirurgicales; 37 % de ces cas sont survenus*

Disclosures Some of this material was presented as a poster at the 37th Annual Meeting of the Association of University Anesthesiologists in Denver, Colorado April 8-10, 2010, at the European Society of Anaesthesiology, Amsterdam, Netherlands June 12, 2011, as well as in an editorial (*Hessel EA 2nd, London MJ*. Anesth Analg 2010; 110: 674-9.)

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pendant l'anesthésie ou la chirurgie et 58 % après l'opération. Par rapport aux cas ne survenant pas en période périopératoire, cette population comptait davantage d'hommes, était plus jeune et était moins encline à avoir un facteur précipitant évident, moins encline à souffrir de douleur thoracique, et moins encline à manifester uniquement une « ballonisation » de l'apex du ventricule. En outre, perioperatoire la CMTT avait une fraction d'éjection plus basse et provoquait une mortalité plus élevée. Le dépistage est facilité par une échocardiographie précoce. Il est possible que l'anesthésiologiste soit témoin d'une CMTT dans d'autres situations, notamment chez des patients subissant d'autres interventions non chirurgicales (par ex. lors d'un électrochoc), chez les patients atteints de conditions aiguës affectant le système nerveux central, ceux atteints de phéochromocytome et dans d'autres maladies graves ou durant des réactions allergiques.

Conclusion *La CMTT périopératoire est plus fréquente qu'on ne le pense et devrait être contemplée chez tout patient hospitalisé présentant un syndrome coronarien aigu et/ou une instabilité hémodynamique, une détresse respiratoire aiguë ainsi que lors d'arythmies cardiaques ou d'arrêt cardiaque.*

Takotsubo cardiomyopathy (TTCM) is a form of stress cardiomyopathy first described in the Japanese literature in 1990[1,2] and in the English literature in 2001.[3] It was initially characterized by a unique pattern of transient wall motion abnormality in the left ventricle characterized by apical ballooning and a hyperkinetic base occurring in the absence of significant epicardial coronary artery disease. It presented like an acute coronary syndrome, most frequently in postmenopausal elderly women, often (but not invariably) triggered by emotional or physical stressful situations. The name "takotsubo" was used because the pattern of wall motion abnormality reminded the clinicians of the shape of a Japanese ceramic pot called a "takotsubo" that is used to trap an octopus (Fig. 1).

While TTCM was initially described in outpatients as presenting like an acute coronary syndrome, it is now reported in hospitalized patients with various medical conditions, especially in critical care units, in patients undergoing various non-surgical procedures, and during the perioperative period. Thus, it is likely that anesthesiologists will encounter TTCM cases under various circumstances (Table 1). The objectives of this narrative review are threefold: first, to provide a general overview of TTCM (i.e., its pathophysiology, diagnosis, and outcome); second, to focus on TTCM in the perioperative period (i.e., management and prevention); and lastly, to review other circumstances in which anesthesiologists may confront this syndrome.

General review of TTCM

Takotsubo cardiomyopathy has at least 75 descriptive names.[4] For this review, I have chosen to use the term "takotsubo cardiomyopathy"[4] because of its familiarity and ubiquitous presence in the literature, even though many cases do not show the classic "takotsubo" pattern of wall

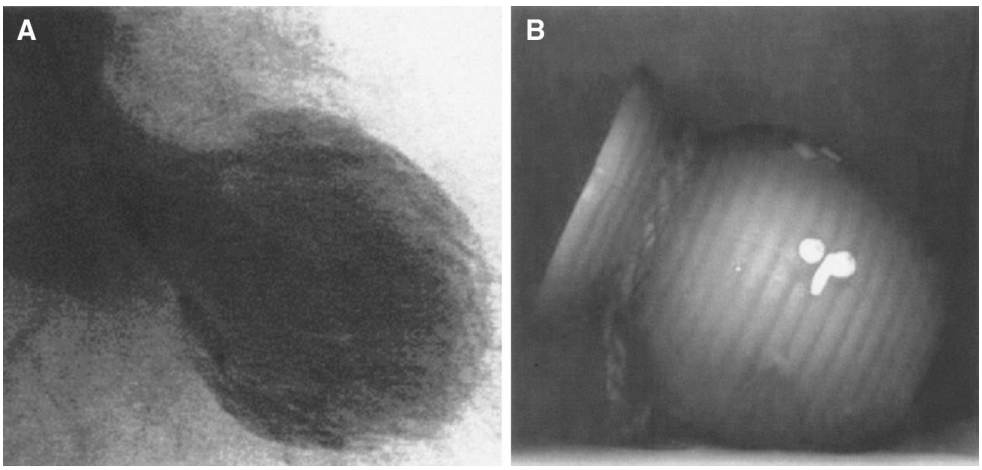

Fig. 1 Ventriculogram and a "takotsubo". (A) Ventriculogram at end systole. (B) A Japanese takotsubo octopus pot trap. From Figure 1 in *Bybee KA, et al.* Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med 2004; 141: 858-65. These figures were adapted from: *Kurisu S, Sato H, Kawagoe T, et al.* Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. Am Heart J 2002; 143: 448-55 and used with permission from Elsevier

Table 1 When/where anesthesiologists may encounter Takotsubo cardiomyopathy

1. Perioperative surgical procedures
2. Diagnostic and non-surgical or minor surgical procedures
a. Electroconvulsive therapy (ECT)
b. Endoscopy: GI and pulmonary
c. Catheterization laboratory
d. Electrophysiological laboratory, including pacemaker implantation
e. Interventional radiology
f. Dobutamine stress echocardiography
3. Acute CNS conditions, especially aneurysmal subarachnoid hemorrhage (A-SAH)
4. Pheochromocytoma
5. Other types of acute critical illness, especially sepsis
6. Allergic reactions, especially anaphylaxis and severe asthma
7. Exogenous epinephrine administration

CNS = central nervous system; GI = gastrointestinal

motion abnormality. The Task Force of the European Society of Cardiology (ESC) prefers the designation "takotsubo syndrome".[5]

In 1915, Dr. Walter B. Cannon (1871-1945), Professor of Physiology at Harvard University, first demonstrated the role of the sympathetic nervous system in the "fight-or-flight" response to stress. Later, in 1942, he published a paper entitled "Voodoo Death" in the journal, *American Anthropologist*. In his paper, he reviewed the many reported anecdotal experiences -mainly in the anthropology literature- of death related to fright and postulated that death was caused "by a lasting and intense action of the sympathico-adrenal system". He hypothesized that this phenomenon was limited to societies in which the people were "so superstitious, so ignorant, that they feel themselves bewildered strangers in a hostile world".[6] The idea that it was limited to primitive societies was dispelled 30 years later in a report of 170 cases, mainly from the USA, of sudden and rapid death during psychological stress.[7] Even earlier, others had called attention to the mortality of bereavement and coined the term "broken heart".[8]

The first description of TTCM that led to the name "takotsubo" was by Dote *et al*. in 1983 at the Hiroshima City Hospital, but the report was not published until 1990 and then only in the Japanese literature.[9] Takotsubo cardiomyopathy has since been observed throughout the world, and in 2006, it was included in the list of acquired primary cardiomyopathies in the "2006 Contemporary Definitions and Classification of the Cardiomyopathies" from the American Heart Association. Nevertheless, it is likely that similar conditions had been described long before the Japanese called attention to this entity in 1990.[10]

Besides the classical "takotsubo" pattern of wall motion abnormality, several other patterns of contraction abnormalities have been reported, including mid-ventricular, basal or inverted, localized, and global hypokinesia; thus, the apical ballooning pattern is no longer considered pathognomonic of the syndrome. Although emotional or physiologic stress precedes the onset of TTCM in 45-85% of cases, this is quite variable. Furthermore, the onset of the stress may precede the presentation by several days, and the degree of stress often does not seem excessive. While the majority of cases occur in adulthood, a number of cases have been reported in the pediatric population.[11]

The ESC has recommended classifying cases of TTCM into two subtypes, *primary* and *secondary*.[5] Outpatients representing the former subtype present with symptoms like acute cardiac syndrome, often precipitated by emotional or physical stressors -classic TTCM. The *secondary* subtype includes mainly hospitalized patients whose TTCM is thought to have been precipitated by their primary medical or surgical conditions, various medical and surgical procedures, or in some cases, anesthesia may have been a contributing factor. Most of the cases that anesthesiologists encounter belong to this *secondary* subtype.

Diagnostic criteria

The diagnostic criteria for TTCM have evolved over time but remain somewhat controversial. The most widely used standard is the revised Mayo Clinic criteria published in 2008[12] as summarized in Table 2. A hallmark of TTCM is complete reversibility of the left ventricular (LV) contraction abnormalities within days to weeks.[13] Several other criteria have been proposed. Recently, the ESC[5] expanded the Mayo Clinic criteria to include new left bundle branch or QTc prolongation as electrocardiogram (ECG) evidence, with small elevations in troponin, significantly elevated brain natriuretic peptide, and demonstration of recovery of ventricular systolic function within three to six months. The criteria also include cases associated with pheochromocytoma.

The "gold standard" in ruling out a primary coronary obstructive etiology is the use of invasive coronary angiography to exclude coronary artery disease, although cardiac computed tomography angiography, magnetic resonance imaging (MRI), and nuclear imaging may also aid in the diagnosis TTCM.[14] An MRI may be helpful in distinguishing TTCM from acute myocardial infarction and myocarditis. Magnetic resonance imaging criteria for the diagnosis of TTCM include: 1) LV dysfunction in a non-coronary distribution, 2) myocardial edema in the region of wall motion abnormalities, 3) increased early myocardial

Table 2 2008 Mayo Clinic criteria for diagnosing Takotsubo cardiomyopathy

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments, with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often but not always present
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin
4. Absence of pheochromocytoma and myocarditis

Modified from *Prasad A, Lerman A, Rihal CS.* Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008; 155: 408-17)[12]

gadolinium uptake (suggesting inflammation), and 4) absence of late gadolinium enhancement, which tends to rule out the scarring that is usually encountered following acute myocardial infarction.[15]

Incidence

The 2008 data from the Nationwide Inpatient Sample in the United States indicated an incidence of TTCM of 5.2/100,000 in females and 0.6/100,000 in males.[16] This incidence appears to have doubled or tripled during 2008-2012[17-19] to about 2-9/100,000 population per year and to account for about 0.08% of hospital stays.[20] The incidence increased with age in females but not in males.[16] Whites were twice as likely to be diagnosed with TTCM as blacks, Hispanics, and Asians. Takotsubo cardiomyopathy is thought to be the cause of 1-2% of patients presenting with symptoms like acute coronary syndrome,[16] more so in females than in males ($\sim 8\%$ *vs* $< 0.5\%$, respectively).[14,21] Dias has called attention to the likely impact of racial differences on the manifestations and course of TTCM.[22]

Pathology

The prototypical pathologic finding in TTCM is contraction band necrosis. It can occur with or without frank myocyte necrosis.[23] Contraction band necrosis is distinct from the thrombosis-related necrosis associated with classic myocardial infarction in that it occurs within minutes, and on hematoxylin and eosin staining, it displays hypercontracted sarcomeres, dense eosinophilic transverse bands, and a mononuclear inflammatory response[24] (Fig. 2). Contraction band necrosis has also been described following subarachnoid hemorrhage, head trauma, near drowning, status epilepticus, victims of violent assault, and numerous other clinical circumstances. It is hypothesized that excess norepinephrine in the myocardium, through cyclic AMP-mediated overload in cytosolic and intramitochondrial calcium, causes excessive contraction.[25]

Pathophysiology and possible pathogenesis

The pathogenesis of TTCM has defied definitive explanation. Clinical features that require explanation include its acute onset (often precipitated by stress triggers), the female predilection, the pattern of contraction abnormalities, and its reversibility. Although a number of hypotheses have been proposed to explain TTCM,[14,26-31] the most widely accepted hypothesis is that TTCM is the consequence of excessive adrenergic/catecholamine stimulation.[30] This results in both direct damage of the myocytes due to the excess intracellular catecholamines and/or indirect ischemic injury due to brief microvascular dysfunction.

Regional differences in myocardial adrenergic receptor density may partly explain the location of the regional wall motion abnormalities observed. An increasing density of β_2 adrenergic receptors from the base to the apex could explain the regional differences in response to high circulating epinephrine levels. Y-Hassan critiques and discounts the hypothesis that high levels of circulating catecholamines are the cause of TTCM and instead favours local cardiac sympathetic nerve hyperactivity with intense release of norepinephrine and spill over as the pathophysiologic mechanism for TTCM.[31] There is also much evidence supporting the hypothesis that a brief period of ischemia due to microvascular dysfunction, perhaps mediated by the sympathetic/catecholamine storm, plays a role in the myocardial injury encountered in TTCM.[32,33]

Other factors that may contribute to the pathophysiology of TTCM include disturbances of calcium homeostasis, estrogen, the emotional state of the patient, depression, the use of antidepressants, and preexisting endothelial dysfunction.[29] It has long been suspected that genetic factors, including certain polymorphisms of alpha- and beta-adrenergic receptors, may explain the susceptibility of certain individuals to stress cardiomyopathy, but conclusive findings are currently lacking.[29,34] The reason for the marked sex discrepancy is unknown,[21] although several hypotheses have been proposed.[29]

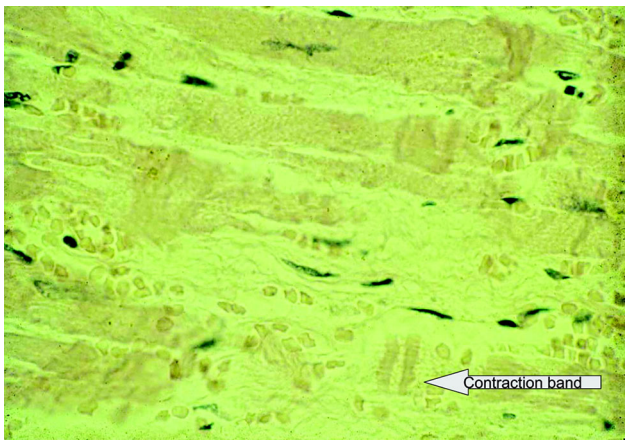

Fig. 2 Contraction band necrosis. The arrows show two of the contraction bands. Reproduced with permission from: *Samuels MA*. The brain-heart connection. Circulation 2007; 116: 77-84[6]

"Stress cardiomyopathy"[35] is closely related. Four stress-related cardiomyopathy syndromes have been described[36]: 1) classic TTCM; 2) LV dysfunction associated with acute intracranial disease such as subarachnoid hemorrhage, which is often termed "neurogenic stunned myocardium"[37,38]; 3) transient cardiomyopathy occurring during other types of critical illness, e.g., sepsis; and 4) transient cardiomyopathy associated with pheochromocytoma and exogenous catecholamine administration. It is likely that these categories represent a spectrum of the same syndrome.

Clinical course and complications

The clinical course of TTCM has been reviewed recently.[5,14,27,28,39-43] Although many patients recover without complications, about 50% experience some complications.[5] Serious complications are not uncommon and include congestive heart failure (12-45%), pulmonary edema (8 to > 20%), and cardiogenic shock (4-20%).[5,20,43-45] In a contemporary series of cardiogenic shock associated with TTCM, the only independent risk factor was a low initial left ventricle ejection fraction (EF), and patients experiencing cardiogenic shock had a much higher 28-day mortality and mortality in the first year following discharge.[45]

Other complications include mitral regurgitation (14-25%),[5] dynamic intraventricular gradients with LV outflow tract obstruction (10-25%),[5] sudden death, syncope, cardiac arrest (4-9%),[5,20,43,46] mural thrombosis (1-8%),[5,43] thromboembolism including stroke (1.6%), ruptured ventricle (< 1%),[5,43,47] and arrhythmias. Arrhythmias occur in up to 44% of patients and life-threatening arrhythmias occur in about 6%,[5,43,48] including atrial fibrillation (5-47%), ventricular tachycardia (1.2-4.0%), ventricular fibrillation (1-2%), and asystole (0.5-3%). About 5% of patients with TTCM experience torsades de pointes tachycardia; longer QTc appears to be a risk factor for life-threatening ventricular arrhythmias.

Mortality

Reported hospital mortality ranges from 0-8%[5,14,26,43,49] and was 4.1-4.5% in three databases/reviews.[20,43,49] Males had a more than twofold higher mortality than females.[20,43,49] Patients with "secondary" TTCM, i.e., thought to have been precipitated by another medical or surgical condition or procedure, have a two- to tenfold higher mortality that those with "primary" TTCM.[18,19,44,49] Among hospital deaths, the cause in 62% of cases was related to the underlying comorbid medical condition, while in 38%, it was directly related to the cardiac complications of TTCM.[49] In the analysis of the International Takotsubo Registry, the only significant independent predictors of in-hospital death were catecholamine use (odds ratio [OR] = 9.7), age > 70 (OR = 2.9), and a physical trigger (OR = 2.8).[50]

Following hospital discharge, Templin *et al*. observed an annual mortality of 5.6%/patient-year, rates of a major cardiac event of 8.2%/patient-year, stroke or transient ischemic attack of 1.7%/patient-year, and recurrence of TTCM of 1.8%/patient-year.[43] Adverse outcomes were twice as high in males. There was no benefit from beta-blocker medication on late survival or on the rate of recurrence of TTCM,[51] but use of angiotensin-converting enzyme inhibitors was associated with improved one-year survival.[43] Another systematic review found the annual recurrence of TTCM to be 1.5% (range 0-13%). The cumulative incidence of recurrence was 1.2% at six months and 5% at six years.[51]

Management

Randomized-controlled clinical trials for the treatment of TTCM are lacking.[52] Thus, management is based mainly on its presumed pathogenesis and pathophysiology. Since patients with TTCM will experience spontaneous recovery of normal cardiac function if they do not succumb to a complication, the objective of therapy is supportive care to sustain life and minimize or treat complications during their spontaneous recovery.[5,26,52] Nevertheless, until an acute coronary syndrome has been ruled out, usually by coronary angiography, management of these patients should be in accordance with having an acute coronary syndrome, including administration of acetylsalicylic acid, heparin, and other antiplatelet drugs with or without fibrinolytics.

Table 3 Factors that define the risk of complications and/or death in cases of Takotsubo cardiomyopathy (European Society of Cardiology)*

Higher risk patients exhibit at least one major risk factor or two or more minor risk factors
Major risk factors
Age ≥ 75 yr
Systolic blood pressure < 110 mmHg
Clinical pulmonary edema
Unexplained syncope, ventricular tachycardia, or fibrillation
Left ventricular ejection fraction < 35%
Left ventricular outflow tract obstruction ≥ 40 mmHg
Mitral regurgitation
Apical thrombosis
New ventricular septal defect or contained left ventricular wall rupture
Minor risk factors
Age 70-75 yr
QTc ≥ 500 msec
Pathologic Q waves
ST-segment elevation persisting ≥ 3 days
Left ventricular ejection fraction 35-45%
BNP ≥ 600 pg·mL^{-1}
NT-pro BNP ≥ 2,000 pg·mL^{-1}
Unrelated ("bystander") obstructive coronary artery disease
Biventricular involvement

* Modified from *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 [5]

BNP = brain natriuretic peptide

The ESC recommends risk stratification to design care for each patient. The Society identifies TTCM patients as being at higher risk of complications and/or death if they exhibit at least one major risk factor or two or more minor risk factors (see Table 3). Also, the ESC suggests that low-risk patients without complications may be discharged early, adding beta-blocker and angiotensin-converting enzyme inhibitors if EF is 35-45%. Higher risk patients deserve intensive monitoring (intensive care or critical care units) for at least 72 hr and often require invasive or noninvasive ventilatory support, advanced cardiovascular support, and even cardiopulmonary resuscitation.[5] Early on, all patients should be monitored by telemetry and observed for heart failure, arrhythmias, and other complications.

It is advisable to conduct early echocardiography to assess LV function, mitral regurgitation, LV outflow tract obstruction, and mural thrombi and also to perform urgent coronary angiography to rule out coronary artery disease. Magnetic resonance imaging can be considered to rule out acute myocarditis, mural thrombi, and right ventricular involvement.

If present, standard treatment of heart failure with angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, and vasodilators is recommended, although a recent large retrospective observational study found no hospital survival benefit from early administration of beta-blockers.[53]

Many advocate anticoagulation in cases where LV thrombi are detected or support anticoagulation in all patients until the akinetic wall motion abnormalities have resolved.[26] A repeat echocardiography is advisable before hospital discharge as well as follow-up one to six months afterward.[5]

Because of the presumed role of excess catecholamines in the pathogenesis of TTCM, avoidance of adrenergic agonists along with the initiation of anti-adrenergic therapy has been advocated.[5,31] Nevertheless, the management of hemodynamic instability in TTCM is somewhat controversial.[45,54] A key initial step is ruling out dynamic LV outflow tract obstruction as its cause, since inotropic support and use of an intra-aortic balloon pump are contraindicated in such patients; however, use of vasoconstrictors, volume therapy, and beta-blockers are recommended.[5,54] If the problem is primary LV failure, it remains unclear whether the administration of inotropic drugs is harmful by worsening the transiently dysfunctional myocardium or whether it delays or impairs full recovery. Granted, most authors consider their use as harmful.[5,38,52] Recent data from the International Takotsubo Registry indicated that use of catecholamines was a strong and independent predictor of in-hospital death (OR = 9.7) and confirmed that catecholamines should be administered with great caution.[50] On the other hand, numerous case reports indicate hemodynamic improvement and full recovery of ventricular function despite use of vigorous inotropic support. A number of authors favour the use of mechanical circulatory support, particularly intra-aortic balloon pumping (IABP) -especially in the presence of severe mitral regurgitation, extracorporeal membrane oxygenation (ECMO), or temporary LV assist devices to minimize or avoid inotropic therapy.[14,45,52,54] Nevertheless, the ESC Taskforce recommends use of extracorporeal membrane oxygenation or temporary LV assist devices instead of IABP for patients with cardiogenic shock associated with TTCM.[5] Some have advocated a preference for use of non-catecholamine inotropic agents (e.g., milrinone, vasopressin, and particularly levosimendan)[5,54,55] over other inotropes for this condition. Unfortunately, controlled data are lacking to compare outcomes of these various therapeutic options. This author considers it reasonable to use mechanical

circulatory support only when the patient is not responding to modest inotropic support.

Because of the possibility of occult pheochromocytoma as the precipitating factor for TTCM, it is prudent to obtain appropriate diagnostic studies in all TTCM patients, or at least in those cases without an obvious cause/trigger, to exclude possible presence of a pheochromocytoma.[52]

Perioperative TTCM

In a number of TTCM case series, 3-23% of cases appeared to have been triggered or precipitated by surgical procedures. This was true in 6.7% of cases in the two large and most recent series.[43,56] Approximately 10% of TTCM cases found in the United States National Inpatient Sample were associated with non-cardiac surgery.[20] In a Japanese database, 16.9% of patients who developed TTCM in the hospital had undergone general anesthesia within the previous seven days.[57] Based on the number of cases of TTCM found in the United States National Inpatient Sample in 2008-2009[20] and the estimated number of surgeries performed in those years, this suggests an incidence of perioperative TTCM of 1/6,700 operations. It is not clear if these cases of perioperative TTCM are triggered by the surgical condition *per se*, the surgical procedure, or the anesthesia.

This author has reviewed case reports/series of perioperative cases identified in PubMed from January 2000-February 2016. Of more than 180 cases identified, only 131 provided sufficient detail to permit inclusion in this review.[58-181] The following section summarizes the findings in these 131 "perioperative cases", and these observations are compared with 1,750 mainly non-perioperative cases (< 7% were post-surgical) in the International Takotsubo Registry.[43]

These 131 perioperative cases were encountered in many different types of surgical procedures, but most commonly in gastrointestinal (16%), cardiothoracic (16%), orthopedic (15%), Cesarean delivery (13%), ear nose and throat and head and neck surgery (10%), and liver (12 cases) and kidney (two cases) transplantation (11%).

Sixty-six percent of these perioperative cases were likely performed under general anesthesia, 10% with spinal, 2% with epidural, 4% with combined general and regional, 3% with local anesthesia, and 5% with no anesthesia. Patients' ages ranged from 5-86 yr, with a mean (standard deviation) of 54 (18) yr. This is significantly lower than the average of 66 yr in the aforementioned International Takotsubo Registry of mainly non-perioperative cases of TTCM.[43] Of the 131 perioperative cases, 40% were < 50 yr of age, which is a much higher proportion than the 13% observed in the International Registry.[43] Also, 80% of patients were female, which is lower than the 90% in the abovementioned International Registry.[43] In the 131 perioperative cases, males averaged 1.5 yr younger than females, while in the International Registry, males averaged four years younger than females.[43]

Seven (5%) of the 131 perioperative TTCM cases occurred prior to induction, 48 (37%) occurred during the anesthetic or surgery, and 76 (58%) occurred postoperatively. Of the intraoperative cases, 54% occurred within the first 20 min, while 9% occurred during emergence. Of the postoperative cases, 63% occurred within the first 24 hr, but 8% occurred more than a week postoperatively.

No precipitating factors were apparent in 44% of these perioperative patients, which is a higher proportion than the 28.5% in the International Registry.[43] In 15% of the 131 perioperative cases, the TTCM was attributed to pain or anxiety, and 5% was attributed to each of respiratory distress/residual neuromuscular blockade or administration of epinephrine. In two cases, the TTCM was attributed to a pheochromocytoma.

Sixty-six percent of the 131 perioperative cases presented with heart failure (e.g., hypotension, dyspnea, hypoxia, pulmonary edema, or low cardiac output), while 36% presented with symptoms of an acute coronary syndrome (e.g., chest pain, ECG changes, troponin release), and 30% presented with cardiac arrest or serious arrhythmias. The level of consciousness of these perioperative patients influenced the pattern of presentation. Fifty-six percent of the perioperative patients were awake, while 44% were unconscious, i.e., under general anesthesia or not yet awake at time of onset. Presentation approximating acute coronary syndrome was more common in awake patients, 41% *vs* 16% in the unconscious patients. In the awake patients, 44% complained of dyspnea, which is similar to non-perioperative cases of TTCM,[43] but only 42% complained of chest pain or discomfort. The latter is much less common than the 76% of non-perioperative patients in the International Takotsubo Registry.[43] Several of these perioperative cases presented immediately prior to urgent or emergency surgery with an acute coronary syndrome that proved to be TTCM. This was true in a recent series of patients with hip fractures.[182] Unique to the perioperative cases encountered by anesthesiologists is that many TTCM cases present while the patient is unconscious. Presentation with cardiac arrest (15 patients) or arrhythmia (18 patients) was more common in the 58 perioperative patients who were unconscious at the time of onset than in the awake patients (57% *vs* 8%, respectively). Sixty-one percent of these unconscious patients also had evidence of low cardiac output, and 25% had evidence of pulmonary edema.

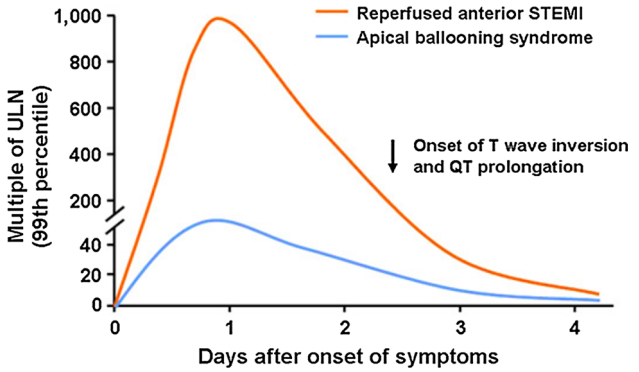

Fig. 3 Comparison of troponin levels after STEMI *vs* TTCM Red depicts levels after anterior STEMI. Blue depicts levels after TTCM ("apical ballooning syndrome"). Reproduced with permission from: *Prasad A, Lerman A, Rihal CS.* Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008; 155: 408-17.[12] STEMI = ST-segment elevation myocardial infarction; TTCM = takotsubo cardiomyopathy; ULN = upper limit of normal

While pre-hospital TTCM typically presents like an acute coronary syndrome, only a minority of perioperative TTCM cases present this way. More often, perioperative cases present with evidence of heart failure, arrhythmias, or cardiac arrest. Thus, one must consider TTCM when any of these signs and symptoms occur during the perioperative period.

The ECG was reported as abnormal in 92% of these 131 perioperative cases. Forty-six percent of the latter exhibited only ST-segment changes, 32% exhibited only inverted T waves, and 18% exhibited both indicators. Amongst the ST-segment changes, 78% were elevated, while 18% were depressed and 4% were undefined. These findings are similar to those in the International Registry.[43] In other reports of all types of TTCM, up to 30% have pathologic Q waves. Over time, 40-70% develop T-wave inversion, and most develop QT prolongation while the ST-segment changes resolve.[183] In general, the ECG in patients presenting with TTCM is indistinguishable from those with acute coronary syndrome.

Troponin levels were reported as elevated in 87% of the 131 perioperative cases, and in 56%, troponin levels were > 1 ng·mL^{-1}. These findings are similar to those encountered in other cases of TTCM. Typically, the troponin elevation is much less (about 1/10th) than one would expect if the wall motion abnormality were due to ST-segment elevation myocardial infarction (STEMI)[14] (Fig. 3); therefore, a high troponin-ejection fraction product differentiates STEMI from TTCM.[184] Although troponin levels are lower with TTCM compared with STEMI and NSTEMI, brain natriuretic peptide levels (BNP) are higher, and a high BNP:troponin ratio has been reported to discriminate TTCM from acute coronary syndrome.[185] The troponin ejection fraction product and BNP:troponin ratios were generally not reported in these 131 perioperative cases.

Sixty-eight percent of the 131 perioperative cases exhibited the classic apical ballooning pattern, which is lower than the 82% in the International Takotsubo Registry.[43] Ten percent of cases displayed the mid-ventricular pattern, and 8% displayed the basal or "inverted" pattern, which was higher than the 2% found in the International Registry.[43] Four percent of cases displayed global hypokinesia, and 7% displayed other patterns of regional wall motion abnormalities.

Initial EF was reported in 73% of 131 perioperative cases, with a median EF of 31% (range 10-60%). The EF was $< 50\%$ in 95% of cases, $< 40\%$ in 79% of cases, $< 30\%$ in 41% of cases, and $< 20\%$ in 9% of cases. This median EF was lower than the 41% reported in the International Takotsubo Registry.[43] Coronary angiograms were performed in only 81% of the 131 perioperative patients.

In these 131 perioperative cases, the surgical procedure was deferred in five of the seven pre-induction cases, while the surgical procedure was aborted in 19 of the 48 intraoperative cases. Management was not described in seven of these perioperative cases. Twenty-five cases were simply observed, while in 99 cases, some type of intervention was implemented, mainly directed at treatment of hypotension/low cardiac output, and pulmonary venous congestion/edema. In these 99 cases receiving interventions, 64% (62/99 patients) received inotropes or vasopressors, 42% (42/99) underwent tracheal intubation and ventilation, 28% (28/99) received mechanical circulatory support (mostly IABP, but several were placed on ECMO), and 24% (24/98) required cardiopulmonary resuscitation. Among the 62 patients who received inotropes or vasopressors, 26 were given norepinephrine, 20 dopamine, 20 dobutamine, 17 epinephrine, four levosimendan, 14 an unnamed inotrope, seven phenylephrine, six vasopressin, and six an unnamed vasopressor. Among the 99 treated, 40% (39/99) were given a beta-blocker, 32% (31/99) diuretics, and 31% (30/99) an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Eight (6.1%) of the 131 perioperative cases died in the hospital, four related to TTCM (three of cardiogenic shock and the other of free rupture of the left ventricle), and the other four probably unrelated to TTCM. One patient died after discharge (unrelated to TTCM). This mortality is somewhat higher than the 4.1-4.5% observed in other large reports of all types of TTCM.[20,43,49] Brinjikji *et al.* observed mortality to be twice as high in cases associated with operating room procedures,[20] but Yerasi *et al.* observed no deaths in 24 postoperative cases of TTCM.[56]

Clinical recovery began within 12 hr in 33% of the 123 hospital survivors. Recovery was complete in 82% by the end of the first week and complete in all hospital survivors by 19 days. Recovery of the regional wall motion abnormalities was complete within the first eight days in 33% of hospital survivors and by one month in 80%.

Long-term outcome was usually not reported in the 123 hospital survivors of perioperative TTCM. Eighteen (15%) survivors were known to have undergone subsequent surgery: ten with general anesthesia, two with spinal anesthesia, two with local anesthesia, and not stated in four. Details of management were mostly not provided. Two of these (11%) patients experienced a recurrence of TTCM perioperatively. Other reports of documented cases of recurrent TTCM due to re-exposure to surgical stress are rare. Interestingly, at least 32 (25%) of these 131 perioperative cases had undergone at least one or more uneventful operations prior to the one associated with TTCM. Five weeks after discharge, one of the hospital survivors of perioperative TTCM experienced an out-of-hospital TTCM attributed to severe emotional distress.

A number of authors have addressed the matter of prevention of an initial episode of perioperative TTCM or in patients who have had a previous episode of TTCM.[38,84,186,187] Many have emphasized the importance of avoiding psychological stress in the perioperative period by use of psychological and pharmacologic approaches, including preoperative deep anxiolysis, adequate level of anesthesia during the procedure, optimal postoperative analgesia and sedation, and administration of prophylactic beta-adrenergic blocking agents. If a patient is recovering from an episode of TTCM, it has been advised to delay elective surgery until myocardial wall motion abnormalities return to normal[38,84] and to give preference to regional anesthesia when possible.[186,187] Nevertheless, due to its relative rarity and lack of randomized clinical studies, these are only opinion-based recommendations, and there are inadequate published data for an evidence-based approach to the prevention of *any type* of TTCM.[5] There is evidence that prophylactic administration of beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers DO NOT prevent TTCM. At the time of their initial episode of TTCM, 18-32.5% of all types of patients who developed TTCM were receiving beta-blockers,[43,188,189] and 43-80% were receiving beta-blockers at the time of recurrence.[188,190] Two systematic reviews found no association between the rate of recurrence and the use of beta-blockers,[51,191] and one found no clinical evidence that angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, and acetylsalicylic acid significantly reduce recurrences of TTCM.[191] Nevertheless, abrupt withdrawal of adrenergic blockers may precipitate TTCM, therefore, it would seem prudent not to discontinue indicated beta-blocker therapy.

Other cases of TTCM that anesthesiologists may confront

Takotsubo cardiomyopathy associated with other non-operative and diagnostic procedures (see Table 1)

In two case series of TTCM, 3-7% of cases were associated with other non-surgical procedures,[3,192] and there are many reports of such cases in the literature.

Takotsubo cardiomyopathy associated with electroconvulsive therapy (ECT)

At least 15 cases of probable TTCM associated with ECT have been reported.[193,194] Interestingly, in eight patients, the TTCM occurred after the patient had previously undergone ECT treatments uneventfully. Only one of the six patients who underwent subsequent ECT treatments had a recurrence of TTCM. Electroconvulsive therapy is known to be associated with a marked rise in catecholamines,[195] and many of the antidepressant drugs that these patients often receive alter neuronal reuptake of plasma catecholamines, which may aggravate this surge of catecholamines.[29]

Takotsubo cardiomyopathy associated with central nervous system (CNS) diseases

Acute CNS diseases are often accompanied with evidence of transient cardiac dysfunction[37,196]; however, the transient LV dysfunction associated with neurologic conditions often occurs in younger patients who experience less chest pain and less ST-segment elevation, and the regional wall motion abnormality is more often global rather than regional. A large number of cases of TTCM triggered by CNS disease have been published,[197] including cases associated with aneurysmal subarachnoid hemorrhage, ischemic stroke, and epileptic seizures.[198] Evidence of temporary cardiac injury is very common in aneurysmal subarachnoid hemorrhage.[199,200] Takotsubo cardiomyopathy occurs in about 8% of aneurysmal subarachnoid hemorrhage, and Finsterer *et al.* reviewed 312 such cases.[201] These data indicate that aneurysmal subarachnoid hemorrhage should be considered a possible cause of TTCM in patients presenting with no obvious trigger, while TTCM should be considered a likely cause of cardiac injury in patients presenting with aneurysmal subarachnoid hemorrhage.

Cardiac dysfunction, which is often reversible, is also common following brain death. Although often global, it is likely a variant of stress cardiomyopathy.[202] Blocking the sympathetic storm associated with brain death may reduce the incidence of cardiac dysfunction in donors,[203] but if it occurs, given time and hormonal therapy (e.g., thyroid, corticosteroids), the heart may recover and be acceptable for transplantation. These hearts may even be successfully transplanted before fully recovered, with subsequent recovery in the recipient.[204,205] This may also apply to potential donors with a heart exhibiting TTCM following cardiac resuscitation in which epinephrine was employed.[206]

Takotsubo cardiomyopathy and pheochromocytoma

The occurrence of TTCM associated with pheochromocytoma adds credence to the hypothesis that excess catecholamines play a central role in the pathophysiology of TTCM. Although the revised Mayo Clinic criteria exclude this perspective from the diagnosis of TTCM,[12] a number of authorities accept cases of reversible myocardial depression associated with pheochromocytoma for this diagnosis.[5] At least 59 cases of TTCM associated with pheochromocytoma have been reported in the literature. Compared with other cases of TTCM, these incidents occur more commonly in males and in younger patients. Moreover, such cases are less frequently precipitated by obvious stressors, exhibit an unusually high incidence of the inverted pattern (32-45%), and show a higher incidence of heart failure and cardiogenic shock. In many cases, the diagnosis of pheochromocytoma was made only after presenting with the cardiomyopathy,[207] as was true in two of the 131 cases of perioperative TTCM reviewed. Thus, pheochromocytoma should always be considered in cases of perioperative TTCM, and appropriate diagnostic testing of all TTCM patients, or at least in those cases without an obvious cause/trigger, is recommended.[52]

Takotsubo cardiomyopathy in other types of critical illness

Acute and reversible LV dysfunction occurs in about one-third to one-half of critically ill patients[36,208] and in about 50% of patients with severe sepsis or septic shock.[209] The ventricular dysfunction is usually global, although many have displayed TTCM patterns of wall motion abnormalities.[209] Critical illness and sepsis are common triggering events for in-hospital TTCM, often associated with high mortality.

Anaphylaxis, allergic reactions, and Kounis syndrome

Transient LV dysfunction syndrome has occasionally been reported during cases of anaphylactic shock and asthma,[210] many of which may represent cases of TTCM. At least 14 cases have been attributed to inappropriate or excessive epinephrine administration.[210,211] Six of these cases exhibited the inverted pattern of wall motion abnormalities, two exhibited the mid-ventricular pattern, and only the minority displayed the apical pattern. Nevertheless, there have been at least five case reports of TTCM associated with anaphylaxis or asthma in patients who did not receive epinephrine. An entity likely related to TTCM is Kounis syndrome, or so-called "allergic angina",[212] defined as the simultaneous appearance of an acute coronary syndrome and an allergic reaction. The echocardiograms in these cases may reveal reversible segmental wall motion abnormalities, including the takotsubo pattern.[213]

Summary

Takotsubo cardiomyopathy is a well-recognized entity that anesthesiologists may encounter in the perioperative setting, during non-operative procedures, and in critical care units. Many cases of perioperative TTCM have been reported, accounting for about 10% of all TTCM published reports, and a greater percent of those present in hospital, with an approximate incidence of one in 6,700 operations. It is likely that the number of hospital cases is underappreciated. In-hospital cases involve younger patients and males more often than out-of-hospital cases, and patients are less likely to present with chest pain and more likely to show signs of heart failure, unexpected cardiovascular collapse, cardiogenic shock, and cardiac arrest. Thus, TTCM must be included in the differential diagnosis of these conditions during the perioperative period. Takotsubo cardiomyopathy can be associated with any type of surgery. Early echocardiography plays a pivotal role in suggesting this diagnosis, but coronary angiography is usually required to rule out an acute coronary syndrome. Inotropic therapy is often required but is somewhat controversial. Finally, the presence of pheochromocytoma should be considered in many of the cases.

Nevertheless, many unresolved issues remain regarding perioperative TTCM, including 1) an explanation for individual susceptibility to TTCM after exposure to a similar degree of emotional or physiologic stress or to a similar dose of exogenous catecholamines that usually does not adversely affect most patients; 2) the cause or trigger in individuals who develop the syndrome in the absence of an

obvious emotional/physiologic stressor; 3) the particular susceptibility of elderly females to this condition; 4) why particular myocardial segments are prone to dysfunction; 5) the optimal therapy during the acute phase and after the patient has recovered, especially in the perioperative period; and 6) the best approach to prevent perioperative TTCM and the ideal anesthetic technique to use in patients who have previously experienced the syndrome (remotely or recently) - in particular, whether there is a role for beta-blocker therapy in managing these patients.[214]

Anesthesiologists should be familiar with how to suspect, diagnose, and manage this syndrome.

Conflicts of interest None declared.

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