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Perioperative Stress-Induced (Takotsubo) Cardiomyopathy in Liver Transplant Recipients

Alexander A. Vitin[1*], Leonard Azamfirei[2], Dana Tomescu[3]

[1] Department of Anesthesiology & Pain Medicine, Department of Surgery, Transplant Surgery Division, University of Washington Medical Center, Seattle WA, USA

[2] Department of Anesthesiology and Intensive Care, University of Medicine and Pharmacy Tîrgu Mureș, Romania

[3] Anesthesiology and Intensive Care Department, "Carol Davila "University of Medicine and Pharmacy, Fundeni Clinical Institute, Bucharest, Romania

Abstract

A comprehensive analysis of published cases of Takotsubo cardiomyopathy, occurred in liver transplant recipients in the perioperative period, has been attempted in this review. Predisposing factors, precipitating events, potential physiological mechanisms, acute and post-event management have been discussed.

Keywors: Takotsubo cardiomyopathy, liver transplant, predisposing factors, precipitating events

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Introduction

Transient acute left ventricular (LV) apical ballooning, also referred to as "Takotsubo syndrome" (TC), is a stress-induced, reversible cardiomyopathy in the absence of coronary artery disease. Stress-induced TC is defined as myocardial infarction (MI)-like syndrome with regressive systolic dysfunction of the septum, apical, posterior and sometimes lateral walls of the left ventricle (LV), with commonly preserved LV basic segments, as well as right ventricle (RV) contractile functions.

According to Proposed Mayo Clinic criteria for TC, the diagnosis required presence of four components:

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 (1).

First reported in Japan in 1991 (2), this syndrome has been described in different clinical settings, including perioperative. Over almost three decades, an awareness of this clinical entity has been steadily increasing. The clinical features and symptomatology, as well as physiology, with emphasis on the role of stress factors, have been thoroughly investigated and well described in more than 200 publications. During the last two decades, more than 140 cases of TC, occurring in different settings, have been reported.

To date, more than 90 perioperative cases have been identified as completely fulfilling the revised Mayo Clinic Criteria. The reported percentage of TC perioperative occurrence in the patients, undergoing general and cardiothoracic surgery, is highest among other types of surgery (about 13.7%), and higher than in the liver transplant (LT) population (about 9%). Female patients comprise the absolute majority (about 86%). Age groups in both genders are almost identical (average of 56.5 year old).

In the LT recipient's population, only about a two dozen perioperative events (mostly in the immediate post-operative period) were categorized as "true" TC, with only a few reports of truly intraoperative TC syndrome, occurred during LT surgery, have been reported to date (3).

* Correspondence to: Alexander A. Vitin, Department of Anesthesiology & Pain Medicine, Department of Surgery, Transplant Surgery Division, University of Washington Medical Center, P.O.Box 356540 1959 NE Pacific street Seattle WA 98195 USA. E-mail: vitin@uw.edu

Stress-induced TC remains a poorly understood, potentially lethal condition, and its' management in the perioperative settings presents a substantial challenge. Even though still being considered a relatively rare complication, perioperatively occurred TC attracts a growing attention of clinicians of many specialties, taking care of LT recipients.

Pathophysiology

Numerous studies have found, that stress-induced catecholamines spike plays a crucial role in the TC physiology. It's been observed that plasma levels of catecholamines during the acute phase of TC were several times higher than those of patients with MI, and remained markedly elevated even a week after the onset of symptoms (4). Increased concentrations of catecholamines, commonly observed in patients undergoing major surgery, specifically epi- and norepinephrine, and their interactions with β-adrenergic receptors in the myocardium may play a significant role in the TC physiology in the perioperative setting for liver transplant recipients.

Lyon et al. [5] proposed, that β1 (positive inotropic effects with norepinephrine) and β2 (negative inotropic effects with high concentrations of circulating epinephrine) adrenergic receptors are unevenly distributed through the myocardium. A relative abundance of β2 receptors in the apical myocardium could explain the tendency for apical suppression with basal sparing during high adrenergic states (i.e. stress) with increased levels of circulating epinephrine. Epinephrine, at high levels, can act as a negative inotrope via ligand-mediated trafficking of the β2 receptor from stimulatory G(Gs) protein to inhibitory G(Gi) protein subcellular signaling pathways (6).

In animal experiments, modeling TC-like conditions, researchers (7) hypothesized, that epinephrine' perceived negative inotropic action represents switching of epinephrine signaling through the pleiotropic β2-adrenergic receptor from canonical stimulatory G-protein–activated "cardio-stimulant" to inhibitory G-protein–activated "cardio-depressant" pathways. They suggested, that agonism of epinephrine for β2-Gs at low concentrations and for Gi at high concentrations could explain the acute apical functional depression, observed in TC, with an apical-basal gradient in β2s explaining the differential regional responses. It's been noted, that norepinephrine does not possess such abilities.

Another group of researchers proposed, that multivessel epicardial coronary artery vasospasm causing ischemia is responsible for reversible left ventricular dysfunction (8). However, the data, supporting this theory, has been limited. In another study, it's been suggested, that coronary microvascular impairment plays a certain role in TC physiology. Using the TIMI myocardial perfusion grade ("Thrombolysis In Myocardial Infarction" study group method), abnormal myocardial perfusion in 69% of TC patients, and perfusion abnormalities, involving multiple coronary territories in 86% of the patients, have been demonstrated. Authors also found a strong relationship between the degree of microvascular dysfunction and severity of myocardial injury (9).

In ESLD patients, several abnormalities in the β-adrenergic signaling pathway have been identified, such as a decrease in β2-adrenergic receptor density, a reduction in Gs proteins, and attenuation of adenylate cyclase activity with resultant decreased cAMP generation (10), all of which affect myocardial contractility on different levels, causing both systolic and diastolic dysfunctions. Patients with cirrhotic cardiomyopathy, among other common features, such as baseline increased cardiac output, attenuated systolic contraction and diastolic relaxation, also demonstrate a reduced response of the heart to direct beta stimulation (β-incompetence) (11). It is unclear, how and to which degree defected adrenergic signaling pathways in cirrhosis contribute in the TC physiology.

It should be stressed, however, that current evidence, supporting any of the proposed underlying pathophysiological mechanisms of TC, is not compelling, and many details of TC physiology, while being investigated extensively, still remain unknown.

Predisposing factors in pre-operative period

A number of stress-related risk factors for TC have been identified in numerous publications. These included mostly physical, physiological or emotional stress. Emotional stress, which is defined as major stress factor for TC in majority of studies, is completely conceivable in immediate pre-operative settings (due to fear of surgery and anesthesia).

A variety of pre-existing co-morbidities have been found to correlate with TC. In large study (12), it's been found that among co-morbidities, also affecting ESLD

population, such conditions as hypertension (58.4%), hyperlipidemia (37.5%), diabetes mellitus (18.9%), history of smoking (13.2%), COPD (18.2%), exhibited the strongest correlation, followed by pulmonary circulation disorders (6.9%) drug and alcohol abuse (3.5% each one).

Pre-existing cirrhotic cardiomyopathy may also play a role in the TC occurrence perioperatively. The prevalence of cardiomyopathies is greater in ESLD patients, than in the general population(13). Findings, suggestive of dilated cardiomyopathy, are also commonly reported from routine echocardiographic screening of transplant candidates. Further, frequent reporting of hypertrophic cardiomyopathy in transplant candidates suggests, that this disorder may also be more prevalent in cirrhotic patients. (14,15). Impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of known cardiac disease (such as coronary disease) are considered typical for cirrhotic cardiomyopathy (16). Typical hyperdynamic circulation in cirrhotic patient due to enhanced sympathetic activity with increased cardiac output and reduced systemic vascular resistance may induce myocardial remodeling and LV hypertrophy (LVH), resulting in systolic and diastolic dysfunction and cardiomyopathy (17). Autonomic dysfunction has been seen in primary biliary cirrhosis and sclerosing cholangitis, and, even without displaying "classical" myocardial dysfunction symptoms, may still be considered an additional risk factor for cardiomyopathy (18). TC has also been reported in 1 case of acute-on-chronic liver failure in patient with ESLD due to hepatitis B, complicated by hepato-renal syndrome, encephalopathy, and high-grade jaundice (19).

Newly diagnosed, significant medical conditions in the ESLD patient may also play a role of physiological stress factor**.** Acute kidney injury (AKI) is considered as one of the most common such conditions. It's been proved, that acute renal failure-associated hemodynamic changes (specifically hypertension), electrolyte imbalance, abnormalities of lipid and carbohydrate metabolism metabolic acidosis, and treatment- associated factors can adversely affect cardiac function (20). Possible mechanisms include changes in the renin-angiotensin-aldosterone levels, an imbalance between nitric oxide production and reactive oxygen species, and inflammation (21). 1 case report of stress-induced cardiomyopathy with AKI (22), followed by a case series of 7 patients with confirmed TC, associated with exacerbation of chronic renal dysfunction or AKI, demonstrated a convincing correlation between acute kidney failure and Takotsubo. (23).

Hemodialysis (HD) is commonly used in treatment of the patients with AKI and hepato-renal syndrome, including perioperative and intra-operative use. It is well recognized, that dialysis patients display substantially higher rates of cardiac morbidity and mortality. Cases of acute, albeit transient, ischemic events, MI, life-threatening arrhythmias, exacerbation of CHF and sudden cardiac death during HD, likely precipitated by the HD procedure, have been reported frequently enough to prove an existence of a causation, rather than just correlation (24,25,26).

Significant hypotension during HD session remains a common event (incidence of 20–30%) (27). It's been shown, that HD is an independent risk factor for the development of both de novo and recurrent heart failure (28). A significant percentage of cardiac mortality appears to be temporally related to the HD procedure, accounting for up to 40% of deaths in this group (29,30). In these cases, reductions in myocardial blood flow, consistent with the development of myocardial ischemia, may have caused myocardial stunning, with resolution after cessation of HD(31). Cases of typical TC during HD sessions have also been reported (32,33).

General intra-operative factors

Emotional strain in anticipation of surgery, procedure itself, and recovery have been recognized as major stressors, causing variety of co-morbidities, ranging from PTSD to catastrophic cardiovascular events. Two groups of intra-operative factors, potentially predisposing to TC, can be identified as surgery-related (pain, hypovolemia/blood loss) and anesthesia- related, some of which are overlapping and difficult to discern. Surgery-related factors are the subject of immediate and ongoing correction, done by means of anesthesia care.

Occurrence of TC has been reported in every stage of anesthesia care: just before general anesthesia (GA) induction (34), during anesthesia induction (35), maintenance, emergence and in the immediate post-anesthesia period. Incidence of TC, occurred at different stages and types of anesthesia, are summarized in the Table1 (modified, from 3).

TC has been observed during or after intraoperative administration of vasoactive agents (adrenalin, phe-

Table 1. Incidence of TC during anesthesia care

Type of Anesthesia	General anesthesia (GA)	65.7
	Local/Regional/Central neuraxial	13.7
	Sedation	4.9
Timing, during GA	Induction	11
	Maintenance	25
	Emergence	6

nylephrine, ephedrine, dopamine, etc.) for hypotension (36,37,38), and atropine for bradycardia (39). In one case, TC was triggered by intraoperative fluid overload and acute hypertensive crisis (40). In the majority of cases, however, identification of anesthesia-related factors, contributing to TC occurrence intraoperatively, remains difficult.

Takotsubo cardiomyopathy during liver transplantation surgery

Liver transplantation surgery presents a variety of factors, that cause a significant cardiovascular stress, such as substantial blood loss, massive transfusions, overall hemodynamic instability, use of high rates of vasoactive agents. Certain major vascular manipulations (portal vein and IVC clamping), and graft reperfusion are among recognized stress factors as well. Cardiac arrest during liver transplantation is a potentially devastating, albeit quite rare complication. In 1995-2006, the reported incidence of intra-op cardiac arrest was 2.1– 3.4% (41,42), went up to 5.5 % in 2013, which may be attributed to increasing percentage of substantially sicker liver transplant recipients. A large retrospective study showed, that intraoperative cardiac arrest occurred most frequently during the neo-hepatic phase (90%). 65.0% of these patients experienced cardiac arrest within 5 minutes, and 35% within 40 minutes after graft reperfusion. Identified causes of intraoperative cardiac arrest included post-reperfusion syndrome (38.2%), pulmonary thromboembolism (35.3%), hyperkalemia (7.4%), and uncontrolled bleeding (7.4%). Prognosis for the patients, experienced intra-op cardiac arrest, was unfavorable: 30-day survival rate was 55.9%, and the 1-year survival rate was 45.6%(43).

To date, only four cases of TC, diagnosed intra-operatively during liver transplantation, have been reported. The data is summarized in the Table 2 (modified from 44).

In two cases, TC occurred around liver graft reperfusion.

In one case, on reperfusion, the ECG revealed peaked T-waves, suggesting hyperkalemia, followed by ventricular tachycardia and asystole. Prolonged CPR, involved 18 rounds of defibrillation, resulted in restoration of perfusing rhythm. Persistent hemodynamic instability necessitated high-rate vasoactive support, and, eventually, IABP insertion. Complete recovery was achieved on POD13 (45). In another case, cardiac arrest occurred during performing the hepatic arterial anastomosis, 15 minutes after completely uneventful portal venous graft reperfusion (ischemia time was only 6h 45m), with stable hemodynamics and absence of acidemia. Authors describe severe, sudden hypotension, refractory to high-dose vasopressors. CPR included numerous cardioversion (200 J) attempts for persistent VT. Subsequent coronary angiography revealed a right dominant coronary system with severe right coronary artery vasospasm and normal flow in the left-sided coronary arteries. Ventriculography showed impaired LV function (EF 35%-40%) with hyperdynamic function of the basal segments and apical ballooning, consistent with diagnosis of TC (46) .

In one of the cases, patient developed pulseless VT immediately after surgical closure in otherwise completely uneventful case. CPR was effective after 60 seconds. TC was diagnosed by TEE upon arrival in the ICU (47).

In one of this review author's case, cardiac arrest occurred to the otherwise hemodynamically stable patient on intra-op HD (for AKI) during the anhepatic stage, following inferior vena cava (IVC) test-clamping and release (44). During liver transplantation, the complete IVC clamping results in a 50%-60% decrease in venous return (48), whereas partial IVC clamp causes variable, about 25–50%, decrease of venous return (49). Significant hemodynamic instability (specifically, more than 30% decrease in MAP or a decrease in cardiac index (50%) during a 5-min test period), following IVC test clamping, is the common indication for initiating veno-venous bypass (VVB) (50). Other indications for VVB include pulmonary hypertension, post-MI impaired ventricular function and cardiomyopathy (51). In this case, VVB was initiated after successful CPR and relatively fast hemodynamic stabilization.

All reported cases bear certain resemblance. TC was identified by TEE in every case, and clinical presentation was similar to that of cardiac arrest, caused by MI in the area of left main coronary artery basin, producing a picture, suggestive of LV lateral and posterior

Table 2. Cases of TC, occurred intraoperatively during liver transplant

Authors /year	Diagnosis	Timing intra-op	ECG changes	TEE findings	Resuscitation		Troponin ng/ml	Recovery /days
					CPR	IA-BP		
Tiwari AK, et al, 2008	NASH	Immediately after graft reperfusion	Peaked T-waves (hyper K+), VT and asystole	akinesis, ballooning mid-, distal, and apical walls EF 10-15%	18 rounds of defib, CPR	Yes	39	12-13
Eagle SS, et al, 2010	NASH MELD 18	15 min post reperfusion during arterial anastomosis	severe sinus bradycardia HR 10 to 20 no ST-T segment alterations	inferior, entire mid and apical LV segments severe hypokinesis EF 35-40%	200J cardiover. for persistent VT	No	5.30	15-16
Harika R.K et al, 2014	ESLD / hemochromatosis and alcohol	After surgical closure	Anteroseptal Q waves, ST elevation, lateral T inversions.	mid-to-distal and apical akinesia. EF25%.	CPR 60 sec. effective	No	0.22- 7.48	5-6
Vitin A. et al, 2017	ESLD, cirrhosis due to PSC; MELD 40, AKI	Anhepatic stage, 5 min after release of test IVC clamp	wide-complex tachyarrhythmia, VF, bradycardia. wide QRS large ST elevations	apex, septum, posterior wall akinesis, LV lateral wall hypokinesis EF 10-15%	CPR 60-90 sec; 200J cardiover. for VF	No	11.37 – 6.06-0.76	3

ESLD, End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; PSC; primary sclerosing cholangitis; IABP, intra-aortic balloon pump

walls akinesis / severe hypokinesis, with apex involvement, and preservation of basal segments and RV shape and function. The CPR was effective in every case, albeit achieved different degrees of perfusion restoration and hemodynamic stability, and no intraoperative demise ensued. Vasoactive agents' choice and infusion rates for hemodynamic optimization were similar in all cases. Troponin levels increase was observed in every case, though never to the magnitude suggesting MI. The surgery was completed in every case. The recovery took place in a span of 6 to 16 days, and all patients (except for one, who died of unrelated reasons) were discharged from hospital. The most obvious differences lay only in the timing of TC occurrence, which suggests potentially lower importance of the particular LT surgery' stage, as compared to wide variety of other intraoperative factors, yet to be identified.

TC IN THE POST-OPERATIVE PERIOD

In 60% of all reported cases, TC has been diagnosed in the postoperative period, with incidence of 37% on post-operative day (POD) 0, 11% on POD 1, and 5% on POD 2 (3). Inadequate pain control, significant hemodynamic instability, necessitated inotropic support postoperatively, as well as a residual neuromuscular block, have been identified as potential precipitating factors for TC occurrence in the postoperative period after non-cardiac/non-transplant surgery. (52,53,54,55).

In large retrospective study (56), included 1460 liver transplant recipients, 17 patients developed cardiomyopathy postoperatively. Median time to onset was 2 days (POD2). 76% of these patients were found to have renal insufficiency; 16 patients out of 17 had a recovery of cardiac function with median EF of 44% at the time of discharge, and 1-year survival rate over 94.1%.

First reported case of the TC in the perioperative settings of LT occurred just 4 hours after uneventful surgery, was diagnosed by bedside TEE. Authors described a moderate hemodynamic instability, followed by fast recovery. (57)

In another case, TC has manifested as cardiogenic shock, on POD 2, 48 hours after uneventful LT surgery and smooth post-op course. After ST segment abnormalities appearance, the patient developed severe cardiogenic shock, that required, along with high rates

of vasopressors, IABP deployment. It took 23 post-op days for the myocardial function to recover enough for IABP removal, and a total of 35 days to achieve an EF of 30%, to start inotropic support weaning process. The patient was discharged on POD 40, with good overall myocardial function, and did well thereafter (58). In similar case, TC occurred postoperatively on POD 1. After 72 hours of high-rate inotropic support, proved inefficient, IABP was inserted and stayed for 9 days. A total cardiac recovery was achieved within 25 days. (59). In two cases-report, another group of authors described a case, where TC occurred late into post-operative period, on POD 18, with 2-days full recovery, without IABP or high-dose inotropic support being necessary. In their another case, patient developed TC immediately after LT surgery, which was uneventful. Severe cardiogenic shock, resulted in non-perfusion hypotension, unresponsive to vasopressors, lead to patient's demise within 24 hours after LT. (60).

One of the distinctive features of TC is a relatively fast reversibility and rapid recovery. It's been observed, that, despite dramatic clinical presentation with cardiogenic shock and arrhythmias, EF improved from 20–49.9% to 59–76% within a mean time of 7–37 days, and complete recovery has been achieved in 95.9% ,with in-hospital mortality rate as low as 1.7% (61, 62).

It appears, that TC manifestation in the post-operative period in the LT recipients provides even fewer warning signs, in comparison to intraoperative events. Almost in every reported case, both the surgery and early post-op period were mostly uneventful, and cardiogenic shock, followed by severe hemodynamic instability, required much longer periods of high-dose inotropic support, IABP deployment and recovery times. The management in every case, choice and timing of interventions dictated by severity of hemodynamic instability, responsiveness to inotropic support, and recovery dynamics. In all reported cases, no immediate precipitating event could be identified, much less predicted.

Conclusions

With only a couple dozen of reported to date proven cases of TC, occurred perioperatively (both intra-and post-operatively) in the liver transplant recipients, no statistical analysis of the possible causes, triggers and predisposing factors is possible at this point. At present time, no sufficient clinical data available to guide the management of TC in liver transplantation population. Prediction, let alone prevention of TC is currently considered unfeasible, and will likely remain so, until better understanding of underlying physiology and precipitating factors are achieved. Further clinical, as well as experimental, research is warranted.

Conflict of interest

None to declare.

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