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Case Conference

Reverse Takotsubo Stress Cardiomyopathy During Liver Transplantation

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Takotsubo cardiomyopathy (TC), also known as stress-induced cardiomyopathy or "broken heart syndrome," is characterized by an acute, reversible ventricular wall motion abnormality.[1] Typical TC involves apical hypokinesis/akinesis and basal hyperkinesis, but anatomic variants have been described, including a midventricular akinesis/hypokinesis and a basal wall motion abnormality, referred to as "reverse TC" (rTC).[1] This is a rare form of TC that has been reported to have distinct clinical and diagnostic criteria. Takotsubo cardiomyopathy has been reported in the perioperative period of major surgeries, including orthotopic liver transplantation (OLT).[2-10]

Timely intraoperative diagnosis of rTC via transesophageal echocardiography (TEE), in the setting of OLT, is challenging. New left ventricular dysfunction, hemodynamic changes, and an altered electrocardiogram can be potentially due to TC or its variants including rTC. The authors present a case of intraoperative rTC during OLT and detail the diagnostic and clinical management.

Case Presentation

A 57-year-old White woman with a history of cryptogenic cirrhosis, status post-OLT 25 years earlier, presented for retransplantation due to chronic rejection. She had a Model for End-Stage Liver Disease score of 35, and underwent transjugular intrahepatic portosystemic shunt 2 days prior to retransplantation. Her acute liver decompensation was complicated by mild encephalopathy, grade 2 esophageal varices requiring banding, and hepatorenal syndrome requiring hemodialysis. The past medical history was significant for hypertension and hypothyroidism. She had no known significant cardiac history and preoperative coronary angiography demonstrated nonobstructive coronary artery disease. Preoperative transthoracic echocardiography demonstrated normal left ventricular ejection fraction of 70%, with no regional wall motional abnormalities and no valvular pathology.

On the day of surgery, the patient was brought to the operating room, standard American Society of Anesthesiologists monitors were placed, and the patient was induced with 2 mg of midazolam, 125 μg of fentanyl, 100 mg of propofol, and 8 mg of vecuronium. After endotracheal intubation with a single-lumen 8.0 endotracheal tube, a right radial arterial catheter was placed, and a TEE probe was inserted atraumatically. Anesthesia was maintained with sevoflurane. A 9-French introducer in the right internal jugular vein was inserted under ultrasound guidance, followed by a pulmonary artery catheter. Given this patient's retransplant status and anticipation of a complex surgery with a potentially prolonged anhepatic phase, and risks of significant blood loss, hemodynamic instability, and cardiac arrest, a venovenous bypass (VVB) was planned. An outflow cannula was placed percutaneously in the right internal jugular vein at the time of central line placement. An inflow cannula was placed by the surgical team via the right femoral vein. Portal vein cannulation was avoided due to

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intravascular thrombosis after transjugular intrahepatic portosystemic shunt placement.

The VVB was initiated prior to hepatectomy. The circulation was supported with the use of vasoactive infusions of phenylephrine, vasopressin, and norepinephrine to maintain mean arterial pressures >65 mmHg. Immediately prior to reperfusion, the patient become acutely hypotensive and premature ventricular contractions were observed on the electrocardiogram. The TEE assessment demonstrated new severe depression of left ventricular ejection fraction of 20%, basal akinesis, and apical hyperkinesis. Additional inotropic support was implemented with intermittent boluses of epinephrine and ephedrine. Hemodynamics stabilized and portal vein reperfusion was tolerated well without further hemodynamic instability. The patient was weaned off VVB and the hepatic artery and biliary anastomoses were uneventful. The graft was reperfused within 7 hours from donor aortic cross-clamp. The intraoperative estimated blood loss was 5.3 liters, and the patient was transfused 10 units of packed red blood cells, 3 units of fresh frozen plasma, 1 pack of platelets, and 2 packs of cryoprecipitate.

The patient was transferred to the intensive care unit while sedated and intubated. High-sensitivity troponin T assay peaked at 478 ng/L, and probrain natriuretic peptide was more than 50,000 pmol/L. Cardiac catheterization ruled out significant obstructive coronary artery disease, and laboratory testing was negative for viral infection. Postoperative transthoracic echocardiography (TTE) demonstrated severely reduced left ventricular ejection fraction of 13%, left ventricular dilatation, and severe mitral regurgitation. Given the clinical presentation, the patient was diagnosed with rTC. Diuretic therapy and a dobutamine infusion were initiated. Hemodynamics improved and the patient was extubated on postoperative day 2, and a follow-up TTE on postoperative day 12 demonstrated improved left ventricular function, with an ejection fraction of 43%, and resolution of mitral regurgitation. The patient was discharged home on postoperative day 25.

Discussion

This report described intraoperative rTC in a patient undergoing OLT. Appropriate diagnosis and prompt clinical management resulted in a favorable outcome. Intraoperative findings of acute hemodynamic changes with acutely reduced left ventricular function in a patient with no history of coronary artery disease should alert the clinician to this potential diagnosis. Takotsubo cardiomyopathy is characterized by an acute, reversible ventricular wall motion abnormality not associated with a specific coronary artery distribution.[1] Although the pathophysiology of TC is poorly understood, it is associated with a sympathetic drive from physiologic or emotional stress, leading to a release of catecholamines and eventual microvascular dysfunction.[11] Takotsubo cardiomyopathy can lead to left ventricular thrombus formation, left ventricular outflow tract obstruction, and mitral regurgitation from systolic anterior movement of the anterior mitral valve leaflet. Takotsubo cardiomyopathy was previously described as a benign condition given its transient clinical course, though its reported mortality is comparable to mortality from acute coronary syndrome.[1] In the United States, hospitalizations with TC as a primary or secondary diagnosis have increased from 75 cases per million adults in 2007 to 259 per million in 2012, likely due to the improved understanding of this distinct entity.[12]

Typical TC involves apical hypokinesis/akinesis and basal hyperkinesis, also described as apical ballooning.[1] It was first reported in 1990 and named takotsubo, which is the term for "octopus trap" in Japanese, due to the distinct appearance of the ventricle. Reverse TC is the most common variant of TC, presenting with basal akinesis and apical hyperkinesis (Table 1).[13] Wall motion abnormalities are transient, with rapid recovery in most patients; however, acute pulmonary edema and profound circulatory collapse have been reported. Intraoperative recognition of TC and rTC depends on a high degree of clinical suspicion and availability of TEE for timely evaluation and management. This cardiac complication may go unrecognized in OLT if TEE monitoring is not adopted or if there is a lack of familiarity with atypical forms of TC. Orthotopic liver transplantation is associated with large fluid shifts, hemodynamic perturbations, increased systemic inflammatory markers, and risk of intraoperative cardiac arrest.[14,15] Intraoperative TEE is used in some centers to understand cardiac function and volume status during OLT. Routine use of TEE is controversial in OLT, as patients often present with esophageal varices, coagulopathy, and thrombocytopenia, thus increasing the risk of an adverse event (eg, esophageal injury, variceal tear, bleeding) with probe insertion. Additionally, the majority of patients have normal preoperative left ventricular function and invasive hemodynamic monitoring is standard. National societies, such as The American Society of Anesthesiologists, Society of Cardiovascular Anesthesiologists, and the American Society of Echocardiography, support the use of TEE in OLT for monitoring ventricular and valvular function.[16] One of the first reports of the use of TEE in OLT was in 1992, in which the authors assessed the suprahepatic inferior vena cava anastomosis.[17] In contemporary practice, TTE is used frequently during OLT. Survey data from high volume liver transplantation centers in the United States reported frequency of intraoperative TEE use in OLT of 87%.[18] A recent position paper by the Society for Advancement of Transplant Anesthesia (SATA) states that the use of TEE during OLT is "an effective form of monitoring with a safety profile similar to cardiac surgery patients," and that "it can improve outcomes in rare, but life-threatening conditions."[19] Currently, there are no standards for training and certification of liver transplant anesthesiologists performing intraoperative TEE. SATA recommends that "all anesthesiologists who use TEE during liver transplant surgery complete formal training pathways that lead to certification by the National Board of Echocardiography;" whereas other authors have proposed that a learning model based on TEE simulation may be more

Table 1
Characteristics of Takotsubo Cardiomyopathy and Reverse Takotsubo Cardiomyopathy[13]

	Takotsubo Cardiomyopathy	Reverse Takotsubo Cardiomyopathy
Proportion of all Takotsubo cases	77-99%	1-23%
Echocardiographic Findings	Transient hypokinesis/akinesis/dyskinesis LV apical segment, basal hyperkinesis Lower LVEF than rTC	Transient hypokinesis/akinesis/dyskinesis LV basal segments, apical hyperkinesis Low LVEF, but tend to be higher than TC
Clinical Characteristics	Older age Less neurologic disease Acute psychiatric episode Chest pain, dyspnea, syncope, nausea, abdominal pain, diaphoresis, indigestion	Younger age More neurologic disease (intracranial hemorrhage, multiple sclerosis) Administration of exogenous catecholamines Chest pain, dyspnea, syncope, nausea, abdominal pain, diaphoresis, indigestion More likely complicated by pulmonary edema/cardiogenic shock
Diagnostic Findings	Absence of obstructive coronary disease on CT or angiography Electrocardiogram changes (ST elevation and/or T-wave inversion), atrial fibrillation Elevation in cardiac troponin Higher levels of BNP and CRP than rTC	Absence of obstructive coronary disease on CT or angiography Electrocardiogram changes (ST depression and/or T-wave inversion), new bundle-branch block, prolonged QT interval Elevation in cardiac troponin
Proposed Pathophysiologic Mechanisms	Sympathetic stimulation/catecholamine surge Unlikely due to coronary artery spasm Estrogen deficiency	Sympathetic stimulation/catecholamine surge Coronary artery spasm Coronary microvascular impairment Estrogen deficiency
Management	Supportive Pharmacologic/hemodynamic support IABP Magnesium sulfate	Supportive Pharmacologic/hemodynamic support Beta blockers for dynamic LV outflow tract obstruction IABP Magnesium sulfate

Abbreviations: BNP, B-type natriuetic peptide; CRP, C-reactive protein; CT, computed tomography; IABP, intraaortic balloon pump; LV, left ventricle; LVEF, left ventricular ejection fraction; rTC, reverse takotsubo cardiomyopathy; TC, takotsubo cardiomyopathy.

feasible and still enhance the acquisition of TEE skills in liver transplant anesthesiologists.[20] At any rate, it is evident that the use of TEE during OLT is being adopted by liver transplant anesthesiologists.

In a recent national database study of 38,740 patients undergoing OLT from 2015 to 2020, the incidence of TC was higher in OLT recipients (0.3%) versus the general population (0.04%).[21] In another comprehensive analysis of individual cases reports of

Table 2
Case Reports of Takotsubo Cardiomyopathy during Orthotopic Liver Transplantation

Author	Sex/Age	Phase of Surgery TC Detected	Presentation	Echocardiographic Findings	Intraoperative Management	Perioperative Course	Comments
Tiwari[8] 2008	F/45	Post- reperfusion	Hypotension, peaked T waves, VT, asystole	Typical TC, TEE placed after hemodynamic instability	Prolonged CPR, IABP, Epinephrine, vasopressin, dobutamine, dopamine, amiodarone	OLT aborted prior to biliary anastomosis. POD 5: IABP discontinued POD12: EF 60%	VVB in place POD 2: successful completion OLT Eventual death due to hemorrhage
Eagle[3] 2010	M/64	Post-reperfusion	Hypotension, VT, bradycardia, ST segment elevation	Typical TC, TEE placed after hemodynamic instability Severe hypokinesis	CPR, Vasopressin, norepinephrine, cardioversion, Transvenous pacing	OLT aborted prior to biliary anastomosis. Cardiac catheterization: severe RCA vasospasm.	No VVB POD 1: successful completion OLT Survived to discharge
Mukhtar[5] 2016	M/48	After induction before skin incision	Hypotension, VT	Typical TC, TTE placed after hemodynamic instability EF 15%	Norepinephrine	OLT aborted	No VVB Successful OLT 40 days later with dexmedetomidine
Elapavaluru[23] 2017	F/70	Anhepatic	PVC	Typical TC, EF 25% TEE placed after induction mitral regurgitation	Vasopressin, norepinephrine	Stable through graft reperfusion IABP in ICU POD 15: tracheostomy	VVB in place Prolonged hospital course POD 38: survived to discharge POD 60: EF 50%
Vitin[9] 2018	M/65	Anhepatic	VT, VF, bradycardia	Typical TC, Severe LV dysfunction TEE placed after hemodynamic instability	CPR, Cardioversion, Vasopressin, norepinephrine	POD 18: normal EF	VVB was started after CPR Survived to discharge

Abbreviations: CPR, cardiopulmonary resuscitation; EF, ejection fraction; IABP, intraaortic balloon pump; ICU, intensive care unit; LV, left ventricle; OLT, orthotopic liver transplantation; POD, postoperative day; PVC, premature ventricular contraction; RCA, right coronary artery; TC, takotsubo cardiomyopathy; TEE, transesophageal echocardiography, VF, ventricular fibrillation; VT, ventricular tachycardia; VVB, venovenous bypass.

TC, 9% of >90 perioperative cases occurred in patients undergoing OLT.[22] Of these, there are very few reports in the literature of intraoperative TC in OLT diagnosed via TEE (Table 2), the majority of described cases occurred postoperatively. Of intraoperative reports, all authors reported normal preoperative echocardiographic findings with no obstructive coronary disease (Table 2).[3,5,8,9,23] TC was associated with substantial hemodynamic derangements, with some necessitating use of an intraaortic balloon pump and cardiopulmonary resuscitation.[3,8,9] Tiwari, Eagle, and Mukhtar described decisions to abort the case to further stabilize the patient prior to transplantation, 2 patients prior to biliary anastomosis, and 1 patient prior to skin incision, with the authors further describing subsequent successful OLT in all 3 patients.[3,5,8] Mukhtar et al. also noted use of dexmedetomidine infusion in the subsequent OLT, started prior to induction of anesthesia, with continued use throughout the case.[5] Dexmedetomidine was used to blunt sympathetic tone, and the surgery was successful without incident.

No cases of intraoperative rTC in OLT have been described, and there are several key findings the authors would like to share. Invasive monitoring tools (ie, arterial line, pulmonary artery catheter, central venous catheter) cannot replace intraoperative TEE for assessing cardiac function at points of substantial hemodynamic instability. There is no other definitive intraoperative method of diagnosing TC or atypical TC. There are several variants of TC, and liver transplant clinicians should be aware of the atypical variety, particularly rTC. Clinical management consists of supportive measures, with escalation of care from pharmacologic to mechanical support. The VVB can be implemented at any point to maintain venous return and provide hemodynamic support, particularly if the consensus plan is to continue with the transplant surgery. Although the liver transplant community seems uncertain about the overall value and indications of VVB, it is a powerful tool in supporting hemodynamics in patients with compromised cardiac function.[24] The literature does not support the use of any specific prophylactic agents, such as beta-blockers or dexmedetomidine, to prevent TC. Pharmacotherapy to decrease sympathetic stimulation should be given in the context of hemodynamic goals.

Conflict of Interest

None.

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