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# Hepatic Artery Thrombosis and Takotsubo Syndrome After Liver Transplantation – Which Came First?

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Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Male, 66-year-old  
**Final Diagnosis:** Hepatic artery thrombosis  
**Symptoms:** Abdominal pain • lethargy • tachycardia  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Transplantology

**Objective:** Rare co-existence of disease or pathology

**Background:** Takotsubo syndrome is a transient, reversible, stress-induced cardiomyopathy that affects only 1.4% of liver transplant patients and can cause complications, including cardiogenic shock, arrhythmia, and thromboembolism. Hepatic artery thrombosis is also rare, affecting just 2–4% of these patients, but can have disastrous consequences. Here, we describe a case of concurrent takotsubo syndrome and hepatic artery thrombosis in a postoperative liver transplant recipient.

**Case Report:** The patient was a 66-year-old man who underwent living donor liver transplantation for non-alcoholic steatohepatitis. On postoperative day 3, he became lethargic and tachycardic to the 120 s. Work-up, including EKG, troponin I, BNP, and transthoracic echocardiogram, was characteristic for takotsubo syndrome. His LVEF of 15–20% was markedly reduced compared to his baseline of 50–55% from 6 months prior. Hepatic ultrasonography showed no hepatic arterial flow, prompting emergent return to the OR, where intraoperative evaluation revealed hepatic artery thrombosis. The graft was salvaged after hepatic artery thrombectomy and arterial anastomosis revision. We are unable to determine which event caused the other in this case, as both takotsubo syndrome and hepatic artery thrombosis manifested within the same time frame.

**Conclusions:** It is important to recognize takotsubo syndrome as a potential cause of cardiac dysfunction and hepatic artery thrombosis in liver transplant patients, and also be aware that hepatic artery thrombosis can precipitate takotsubo syndrome.

**MeSH Keywords:** Hepatic Artery • Liver Transplantation • Takotsubo Cardiomyopathy

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## Background

Takotsubo syndrome (TS) is a transient, reversible, stress-induced cardiomyopathy. For diagnosis, all 4 of the following Mayo Clinic diagnostic criteria must be met: 1) transient left ventricular systolic dysfunction, 2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, 3) new electrocardiographic abnormalities or modest elevation in cardiac troponin, and 4) absence of pheochromocytoma or myocarditis [1,2]. EKG changes can include transient ST-segment elevation, non-specific T-wave abnormalities, or new bundle-branch block [2]. The new EKG abnormalities and elevated cardiac troponin necessitate inclusion of myocardial infarction in the differential diagnosis [2]. Echocardiograms classically show apical ballooning in TS [1,3]. Physical, physiological, and emotional stress are risk factors that can precipitate TS [1].

TS has most commonly been reported in elderly women with neurological or psychiatric disorders, but is increasingly being reported in postoperative patients [1,4]. Recently, several case series and retrospective studies have described TS in liver transplantation (LT) patients in the perioperative period [1,5]. In a retrospective, single-center study of 1752 liver transplants, the incidence of TS was found to be 1.4% [6]. Only about 2 dozen cases of TS occurring in the perioperative or intraoperative phases of a LT have been reported to date [1]. Case reports of TS in LT patients include 1 patient requiring a left ventricular assist device (LVAD) after failing inotropic and vasopressor therapy [7], patients who had a cardiac arrest due to TS [8,9], and another patient who experienced TS intraoperatively during the anhepatic stage of liver transplant [10].

TS can be associated with hypercoagulability. In fact, thromboembolism has been diagnosed in approximately 4% of TS patients [11]. In LT patients, thrombosis can be particularly devastating. Hepatic artery thrombosis (HAT) occurs rarely following liver transplantation, affecting only 2–4% of patients, but can lead to disastrous complications, including graft loss and patient death [1,12,13]. Well-known risk factors for HAT are related to surgical technique and longer cold ischemia times [1,12]. Other risk factors include pre-existing conditions such as inherited thrombophilia, acute intermittent porphyria, and primary sclerosing cholangitis [14].

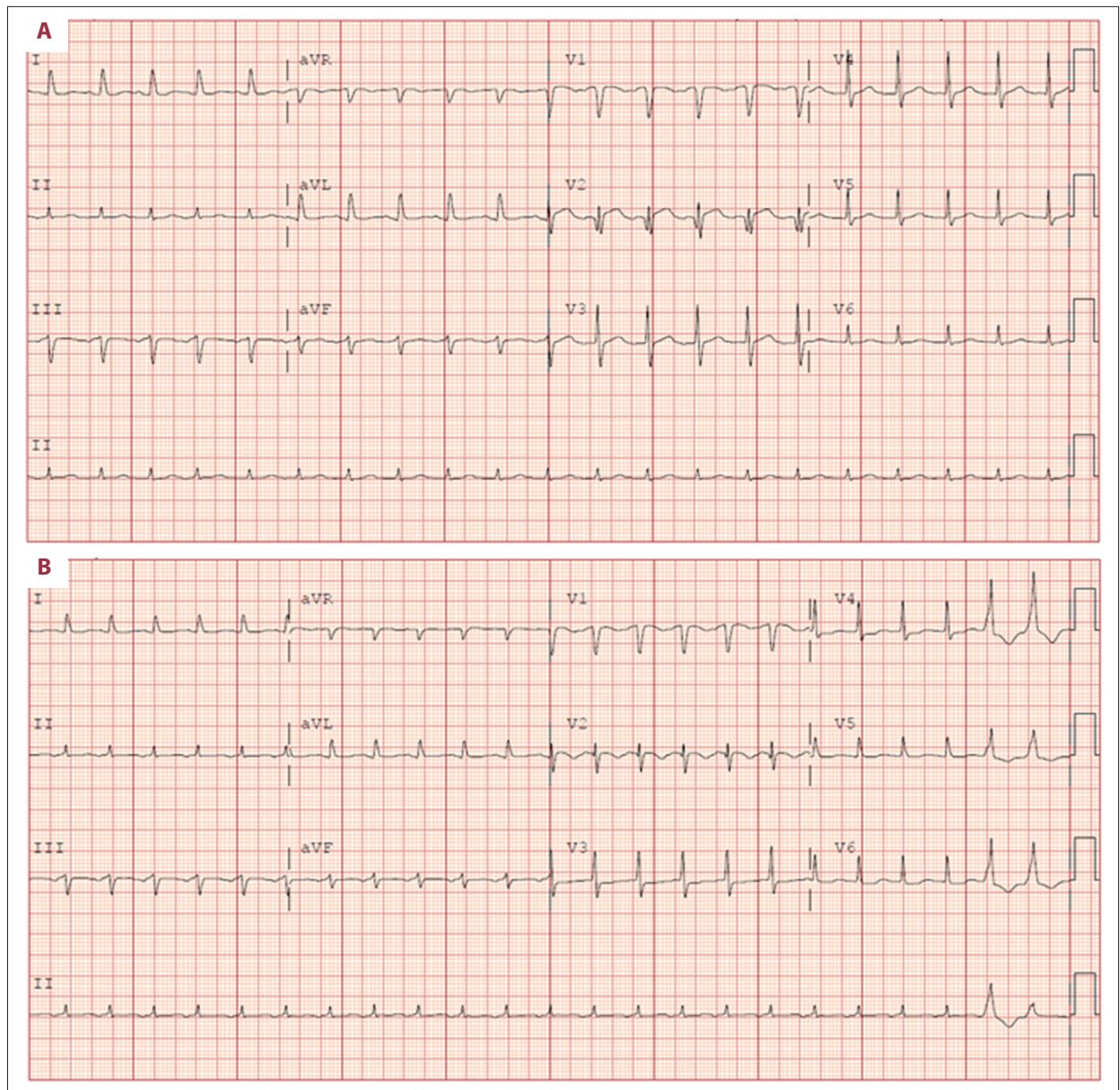
There has only been 1 previous report of a patient developing HAT in the setting of TS after LT [15]. Our patient is the second reported case of this phenomenon. In the absence of the above-stated risk factors, it is possible that TS was the precipitating factor for HAT formation in our patient after liver transplantation. However, the converse is also feasible – that HAT formation led to a stress response that triggered development of TS.

## Case Report

Our patient was a 66-year-old white man with end-stage liver disease (ESLD) related to non-alcoholic steatohepatitis (NASH), complicated by hepatic encephalopathy, esophageal varices, ascites, lower-extremity edema, and fatigue. Other past medical history includes type 2 diabetes mellitus, irritable bowel syndrome, and recurrent *Clostridium difficile* diarrhea. A pharmacological stress test 5 months prior to surgery showed no electrocardiographic evidence of myocardial ischemia, with normal left ventricular perfusion, no evidence of inducible ischemia, and a Duke Treadmill Score of 6. His past surgical history included left inguinal hernia repair with mesh 7 months ago and sigmoid resection for diverticulitis 23 years ago. He had never smoked and did not drink alcohol.

He received a living donor LT for his ESLD. On the day of his transplant, his MELD score was 15 (calculated from serum creatinine 0.9 mg/dL, serum sodium 131 mmol/L, total bilirubin 3.2 mg/dL, and INR 1.5) and his Child-Pugh score was 12 (with albumin 2.2 g/dL). His operation was notable for significant adhesions. He also experienced hypokalemia and supraventricular tachycardia intraoperatively, which improved after potassium repletion and bolus diltiazem. Estimated blood loss was 7.5 L. Intraoperatively, he received 7 units of RBCs, 16 units of FFP, 2.5 L of cell saver, 3 L of albumin, 2 units of cryoprecipitate, 3 units of platelets, and 100 mL of 25% albumin. He was admitted to the Surgical Intensive Care Unit (SICU) following the operation, intubated and in stable condition.

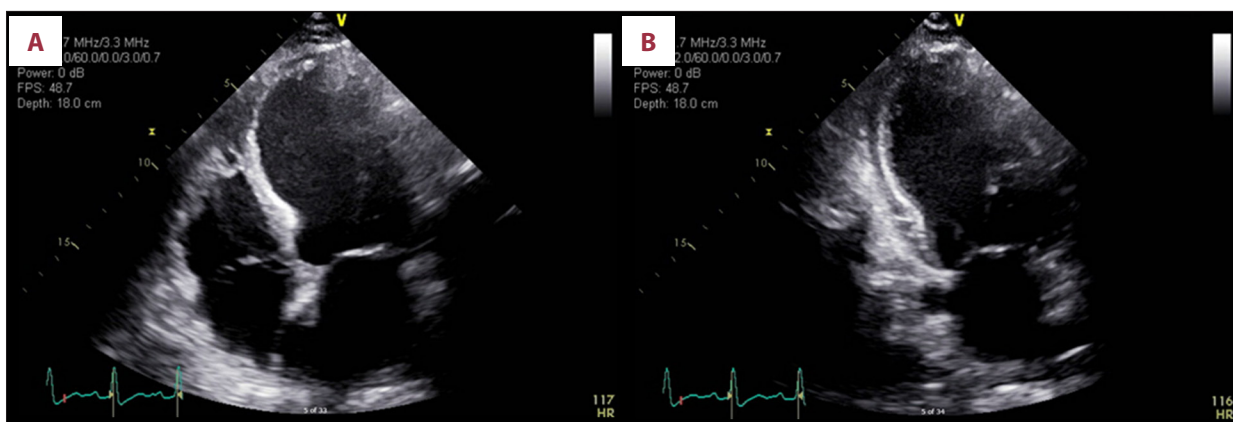
Doppler ultrasound of the liver on postoperative day (POD) 1 showed patent vasculature. He was extubated later that day and transferred to the Transplant Intermediate Care Unit on POD2. He received opioids for his abdominal pain, resulting in depressed respiratory rate and subsequent administration of naloxone. Early the morning of POD3, he developed bradypnea, lethargy, and sinus tachycardia to the 120 s. EKG at this time showed ST elevations in V2 (Figure 1A). He had a troponin I elevation to 0.45 and BNP of 1660. Aside from a hemoglobin level of 7.8 immediately post-operatively on POD0, his hemoglobin level had been consistently above 8. A TTE was then performed, revealing global hypokinesis and a left ventricular ejection fraction (LVEF) of 15–20% (Figure 2), which was markedly reduced compared to his prior known baseline of 50–55% from 6 months prior (Table 1). Throughout these events, the patient denied any chest pain, chest pressure, palpitations, dyspnea, lower-extremity edema, or lightheadedness. He was started on milrinone for inotropic support. He also complained of RUQ abdominal pain. Morning labs revealed a rise in bilirubin and liver transaminases with persistently elevated INR and leukocytosis (Table 2), so hepatic ultrasonography was performed, which was unable to identify hepatic arterial flow. As a result, he was emergently taken to the OR for exploration.



**Figure 1.** EKGs reveal transient ST elevations in V2 that were present on POD3 (A) and resolved by POD4 (B).

Intraoperative evaluation revealed hepatic artery thrombosis limiting blood flow to the transplanted liver, so the arterial anastomosis was revised and the patient was given tPA and several rounds of heparin intraoperatively. The bile duct was ligated to allow access and was left in discontinuity. At the conclusion of this operation, a pulse could be palpated through the hepatic artery, but no Doppler signal was present. His skin was closed but his fascia was left open and his abdomen was packed with the intention of performing a second-look operation for POD6 and evaluating at that time whether to relist him for transplant. He was readmitted to the SICU following the operation, intubated and in stable condition.

However, on POD4 and onwards, ultrasounds demonstrated a patent hepatic artery and LFTs were downtrending (Table 2). On POD4, his troponin I level peaked at 0.97; a repeat TTE showed improved LVEF, and a repeat EKG showed resolution of ST elevations (Figure 1B). On POD6 he returned to the OR for removal of a laparotomy sponge previously left intentionally for packing, reconstruction of his biliary anastomosis, and closure of his abdomen. His heart function continued to improve and the milrinone was discontinued on POD8. TTE on POD9 showed improved LVEF to 45%, and by POD13, LVEF had returned to the baseline of 50–55% (Table 1). He was discharged on POD23 to a transitional care hospital and instructed to take metoprolol and lisinopril for 3–6 months.



**Figure 2.** TTE on POD3 shows global hypokinesis and revealed LVEF 15–20%. The apical 4-chamber view can be seen in **A**, and the apical 2-chamber view can be seen in **B**.

**Table 1.** LVEF.

Date	LVEF
6 months prior to operation	50–55%
POD3	15–20%
POD9	45%
POD13	50–55%

## Discussion

This patient had EKG changes and troponin leak in the setting of new-onset compensated cardiomyopathy. His differential diagnosis included takotsubo syndrome (TS) and obstructive coronary disease. The transient new ST elevation seen in lead V2 on POD3 (Figure 1A), which resolves by POD4 (Figure 1B), was consistent with TS. ST elevations are actually the most commonly seen EKG abnormalities in TS [2]. Echocardiogram revealed global hypokinesis (Figure 2), which is a rare presentation of TS [16]. These changes, along with the fast reversibility and rapid recovery of LVEF in the setting of known stressors, which included major surgery and blood loss necessitating transfusions, led our cardiology team to believe TS was the most likely diagnosis in this patient. It is important to note that obstructive coronary disease cannot be completely ruled out in this patient, because he never had a coronary catheterization performed. In addition, tPA was administered due to concern for HAT. Patients with NASH are at a higher risk for coronary artery disease (CAD) [17]. However, our patient had a negative stress test result pre-operatively, which indicates he did not have severe CAD. The patient's EKG abnormalities did not fit the STEMI criteria, which require ST elevation >2 mm in at least 2 contiguous precordial leads. Therefore, with his troponin leak, we could consider NSTEMI as a possible diagnosis, either type 1, which is due to an obstructive cause, or type 2, which is due to ischemia. However, the patient's EKG

**Table 2.** LFTs before (POD3) and after (POD4) hepatic artery thrombectomy and arterial anastomosis revision.

Date	AST	ALT	INR
POD0	199	181	1.4
POD1	197	223	2.2
POD2	142	219	2.0
POD3	305	388	1.8
POD4	123	164	1.7

lacked persistent pathological Q waves (Figure 1), so an infarct did not occur in this patient. In addition, the wall motion abnormalities seen on echocardiogram were in a non-coronary distribution. Although it is plausible that blood loss during the LT operation necessitating blood transfusion could have caused demand ischemia, the patient's hemoglobin was above 8 (the transfusion goal for patients with heart disease) at the time of significantly reduced LVEF on POD3, making this diagnosis less likely.

TS is known to be associated with stress-related risk factors, but the exact pathogenesis of the condition remains unknown. It is thought that emotional or physical stress causes high catecholamine concentrations in the body that induce microvascular spasms and interact with beta-adrenergic receptors in the myocardium to cause myocardial stunning [1,10]. ESLD patients have defective adrenergic signaling pathways that affect myocardial contractility and can contribute to the TS physiology [1].

Patients undergoing major surgery often have increased concentrations of catecholamines, which can precipitate the occurrence of TS due to many factors [1]. Anticipation of surgery causes emotional strain [1]. Pain, blood loss, and anesthesia

can also predispose to TS [1]. Liver transplantation surgery in particular provokes a large amount of stress on the cardiovascular system due to hemodynamic instability, substantial blood loss necessitating massive transfusions, major vascular manipulations such as vessel clamping, and graft reperfusion during surgery [1]. Our patient not only experienced these stressors that affect all liver transplantation patients, but also developed hepatic artery thrombosis (HAT) after his transplantation. This HAT formation may have led to a stress response that contributed to the development of TS.

TS is often self-limited and 90% of the time resolves completely without an adverse event. Most patients recover their normal heart function in 3–16 days [10], and there is a low in-hospital mortality of just 1.7% [1]. However, TS can result in significant morbidity and mortality in critically ill patients such as LT recipients, in which the estimated mortality rate is 10–27% [4]. Complications from TS include “acute stroke, cardiogenic shock, arrhythmia, thrombus formation, left ventricular outflow tract obstruction, pericarditis with effusion, and ventricular wall rupture” [4]. In transplant patients, these adverse events can compromise the allograft and lead to death [4,18].

It has been postulated that TS is associated with hypercoagulability, as high catecholamine levels may cause vasoconstriction, platelet activation, and other prothrombotic effects [11]. Interestingly, our patient is only the second ever reported case of HAT in the setting of TS. HAT is an uncommon but catastrophic complication after liver transplantation that can lead to early graft loss or even patient death [13]. Only 10% of organs can be saved once HAT occurs [13]. In the only other reported case of HAT and TS, the patient developed TS on POD4, which likely contributed to HAT formation several days later, and he died on POD22 [15].

Well-known risk factors contributing to HAT are related to surgical technique and longer cold ischemia times [1,12]. However, our patient did not have a challenging or prolonged arterial reconstruction. Each time he went to the OR, examination showed the artery was not kinked. Ultrasound of his liver on POD1 showed patent vasculature, indicating that there were no immediate problems with the anastomoses. There was no prolonged cold ischemia time either, as he had a living donor LT with the donor liver brought into the OR for transplantation immediately after donor hepatectomy. In review of our patient’s medical history, he notably did not have pre-existing conditions such as inherited thrombophilia, acute intermittent porphyria, or primary sclerosing cholangitis. Because we are unable to identify any technical issues that may have led to HAT formation, it is possible that TS may have been the precipitating factor for HAT formation in our patient. TS resulting

in his low EF of 15–20% likely created a situation in which he had decreased blood flow velocity. This scenario, along with his limited mobility due to abdominal pain, increased the opportunity for thrombosis. Luckily, our patient was able to undergo thrombectomy upon return to the OR, which restored patency of the hepatic artery and his graft was salvaged, allowing him to avoid the need for re-transplantation.

Treatment for TS depends on severity and patient response to therapies. Strategies specific to managing acute left ventricular dysfunction in LT patients are not well-defined, but in general, first-line treatments for low cardiac output are diuretics, inotropic therapy, and vasopressors [5,7,19–21]. If there is decreased perfusion secondary to vasoconstriction, first-line treatment should include vasodilators [22]. Of note, epinephrine should be avoided in patients with TS because it causes catecholamine release, which can worsen the symptoms by triggering microvascular and myocardial dysfunction [11,23]. If medical management fails, “intra-aortic balloon pumps, left ventricular assist devices, and extracorporeal membrane oxygenation” should be considered for circulatory support [4,7,11]. Fortunately, our patient responded well to inotropic therapy and did not require more invasive interventions.

We do not yet have a way to prognosticate a patient’s risk for developing TS. To date, no studies have been able to identify precipitating events that can predict the development of TS in LT recipients [1,5,6]. Therefore, it is important for surgeons to be aware of TS as a potential cause of cardiovascular dysfunction in LT recipients, especially as TS can contribute to potentially lethal complications, including HAT. It is also important for surgeons to maintain a high level of suspicion for TS if the patient develops cardiac dysfunction after HAT.

## Conclusions

It is important to recognize takotsubo syndrome as a potential cause of cardiac dysfunction and hepatic artery thrombosis in (LT) patients [24]. It is equally important to recognize that hepatic artery thrombosis can cause stress that triggers the development of takotsubo syndrome. At this time, we do not have a reliable way of predicting which patients have a higher risk of developing TS [10]. This is likely due to our limited understanding of the pathophysiology driving TS [10]. Therefore, more research must be conducted to elucidate this information so that we can better manage TS and its complications in critically ill patients.

## Conflict of interest

None.

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