Acute right ventricular failure after orthotopic liver transplantation

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Abstract: The interdependence between the heart and liver in maintaining hemodynamic stability during the perioperative period of either orthotopic heart (OHT) or liver (OLT) transplantation is important. The pre-transplant hemodynamic changes that occur in patients with end-stage liver disease (ESLD) can include decreased systemic vascular resistance, poor ventricular response to stress and increased cardiac output (CO). Concomitant pulmonary disorders are often present in ESLD. Portopulmonary hypertension (PoPHTN) is an important marker for increased mortality in liver transplant patients. The pathophysiologic mechanisms specific to PoPHTN have been compared with other known forms of pulmonary hypertension, including primary pulmonary hypertension, and has been found to fall within a spectrum of disorders related to factors both due to intrinsic liver failure [with resultant portal hypertension and hepatopulmonary syndrome (HPS)] as well as pulmonary vascular remodeling. We present a 47-year-old Caucasian female with ESLD secondary to non-alcoholic steatohepatitis and HPS. Our current case demonstrates the difficulty in managing patients with acute pulmonary hypertension after OLT. Review of the contemporary literature demonstrated a total of eight case reports of post-transplant severe pulmonary hypertension thought to be due to a combination of either HPS or PoPHTN. This case highlights the complexities of patient management in the acute setting after OLT. Furthermore, it demonstrates the intricate role of careful preoperative evaluation and screening in patients undergoing workup for solid organ transplantation.

Keywords: Right ventricular failure (RV failure); portopulmonary hypertension (PoPHTN); hepatopulmonary syndrome (HPS); orthotopic liver transplantation (OLT)

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Introduction and background

The interdependence between the heart and liver in maintaining hemodynamic stability during the perioperative period of either orthotopic heart (OHT) or liver (OLT) transplantation is important for long-term success (1). As systems which work in parallel, the venous return through the liver can carry with it proinflammatory cytokines that have been shown to have a direct effect on both systolic and diastolic cardiac function (2).

Cardiac evaluation prior to liver transplantation plays a key role in identifying modifiable risk factors with the goal for optimizing patients prior to surgery (3,4). The pre-transplant hemodynamic changes that occur in patients with end-stage liver disease (ESLD) can include decreased systemic vascular resistance, poor ventricular response to stress and increased cardiac output (CO) (5).

To appropriately simulate the hemodynamic and loading conditions that occur during liver transplantation, dobutamine stress echocardiography is the most widely used screening tool for risk stratification in the ESLD population. Other investigations that are performed for standard preoperative evaluation are the right heart catheterization (RHC) as well as myocardial perfusion imaging and coronary angiography (6).

Concomitant pulmonary disorders are often present in ESLD. Portopulmonary hypertension (PoPHTN) is an important marker for increased mortality in liver transplant patients. Moderate to severe pulmonary hypertension, defined as a mean pulmonary arterial pressure (mPAP) on

RHC of 35–45 mmHg should be evaluated further with vasodilator challenge. Positive response to vasodilator therapy is favorable and associated with improved outcomes after OLT (7). The presence of PoPHTN is estimated between 5% and 9% of all patients evaluated to undergo liver transplant (8,9).

The pathophysiologic mechanisms specific to PoPHTN have been compared with other known forms of pulmonary hypertension, including primary pulmonary hypertension, and has been found to fall within a spectrum of disorders related to factors both due to intrinsic liver failure [with resultant portal hypertension and hepatopulmonary syndrome (HPS)] as well as pulmonary vascular remodeling (10). A pertinent fact that is often seen after OLT is the resolution of HPS, however, the effect of this on PoPHTN has not been well described. Multiple circulating vasoactive substances have been postulated to cause a number of downstream effects including arteriolar remodeling, pulmonary vasoconstriction and endothelin receptor activation leading to increased endothelin concentrations (11).

Furthermore, those patients with untreated PoPHTN have higher rates of mortality. This mortality is improved with liver transplantation and judicious management of the right ventricle (RV) and pulmonary arterial pressures in the postoperative period. This last area of clinical management is the focus of our case presentation and subsequent discussion and review of the current literature.

Case presentation

We present a 47-year-old Caucasian female with ESLD secondary to non-alcoholic steatohepatitis and HPS. Her preoperative evaluation included trans-thoracic echocardiogram (TTE) as well as Dobutamine stress echocardiogram (DSE) and RHC. During her pre-transplant workup her TTE showed normal biventricular function and size with the presence of intrapulmonary shunt on contrast enhanced echocardiogram. Her pulmonary artery (PA) systolic pressure was measured to be <30 mmHg. Her initial RHC was done at an outside facility and her mPAP was noted to be <35 mmHg. There were no signs of transient ischemic dilatation or regional wall motion abnormality on her DSE. Her coronary angiography showed no obstructive lesions. It was thought that the patient had HPS due to the presence of platypnea and orthodeoxia, as well as brisk CO of 6–8 L/min and index of >4 L/min at rest. As a result of the pre-transplant workup she was listed for transplant and underwent a successful liver transplantation with an uneventful postoperative course. She was discharged on standard immunosuppressive therapy.

The patient did well and was seen in clinic regularly. She was noted to be compliant with her medical therapy. During her 2-month follow-up visit, it was noted that the patient had developed increasing abdominal girth and worsening dyspnea at rest and exertion. She endorsed New York Heart Association Class 3 symptoms. Her abdominal distention was thought to be secondary to ascites. Her tacrolimus level was within the therapeutic range and her transaminases, total bilirubin and alkaline phosphatase were only minimally elevated. She was sent for further workup and post-transplant TTE showed acutely dilated RV with severe RV dysfunction and an estimated RV systolic pressure of 75 mmHg. With concern for pulmonary embolism (PE) a ventilation/perfusion scan was done, resulting a low-probability for PE. Due to the acute decompensation during her first 2 hospital days, an urgent RHC was performed and showed RA pressures of 16 mmHg, PA pressures of 96/41 mmHg with mPAP of 60 mmHg. Her pulmonary capillary wedge pressure (PCWP) was 30 mmHg, indicating elevated left sided filling pressures as well. Her pulmonary vascular resistance (PVR) was calculated at 13 wood units.

After obtaining the above RHC data, the patient was aggressively diuresed and started on intravenous (IV) inotrope support with Milrinone. Titration of milrinone to 0.5 mcg/kg/min had little effect. With progressively worsening clinical status, the patient was started on IV phosphodiesterase 5 (PDE5) inhibitors which helped marginally. The patient eventually underwent placement of a percutaneous right sided ventricular assist device via the Impella RP (Abiomed, Danvers MA).

The Impella RP provided an estimated 4 L/min of flow at maximal power settings and was used as a bridge to recovery in hopes to offload the RV and overcome the patient's severe pulmonary hypertension (the patient's left-ventricular end-diastolic pressure at the time of Impella RP placement was noted to be 9 mmHg during simultaneous pressure recordings). To further evaluate and manage the patient, high output states such as anemia and thyrotoxicosis were ruled out. Repeat RHC showed persistent elevation in the patient's mPAP, however, her PCWP was <15 mmHg which brought to light the possibility of unmasked PoPHTN.

Due to progressively worsening hypotension and the patient's wishes, care was withdrawn, and the patient was allowed natural death. No post-mortem examination was performed.

Discussion

Our current case demonstrates the difficulty in managing patients with acute pulmonary hypertension after OLT. Review of the contemporary literature demonstrated a total of eight case reports of post-transplant severe pulmonary hypertension thought to be due to a combination of either HPS or PoPHTN (12,13). As in the previously reported case series, our patient likely had underlying PoPHTN at the time of evaluation, which was masked by her HPS and contributed to her liver dysfunction that was expected to have reversed after OLT. As a result of transplantation and removal of the diseased liver and the decrease in potential vasoactive substances—specifically those affecting the endothelin and nitric oxide pathways—may have resulted in less available nitric oxide and increased amounts of endothelin. This cascade of events can potentially be linked to the unopposed pulmonary vascular constriction, unmasking pulmonary hypertension at a time during or just after OLT.

Furthermore, the delay in presentation of previously reported cases of acute pulmonary as well as portal hypertension of up to 18 months in one study (13) may be related to anti-rejection medications, specifically tacrolimus. A study by Kamath *et al.* showed that the concentrations endothelin-1 (ET1) were greater in the portal versus hepatic circulation in patients with PH. Additionally, explanted livers in cirrhotic patients were found to have an increased histochemical concentration of ET1 within the lining of the portal vein when compared to those patients without PH and normal livers (14,15). It has also been previously described that increased concentrations of ET1 are present in patients with idiopathic portal hypertension (IPH) (16).

As a result, the ET1 pathway has garnered significant interest in the management of directed therapies for pulmonary hypertension. Recent reports and one study currently underway may shed light into the possibility of bone morphogenic protein receptor type II (BMPR2) and its role in PoPHTN and pulmonary hypertension. Specifically, considering tacrolimus therapy for the reversal of pulmonary hypertension has been proposed by way of increasing BMPR2 signaling pathways (17). As a TGF-beta family of receptors, multiple vasoactive substances have effects on downstream signaling via the cyclic-GMP or cyclic-AMP pathways (18,19).

Based on our patient's presentation as well as the mechanistic actions of her immunosuppressive regimen, it may be plausible for our patient to have had underlying PoPHTN which was balanced by her HPS. As a result of transplantation, removal of her native vasoactive peptides and resultant unopposed pulmonary constriction she presented in acute to subacute RV failure. The delay in her presentation and partial response to therapies during her hospitalization may have been augmented by the anti-proliferative properties of her tacrolimus (17-19). Unfortunately, due to the lack of post-mortem examination, no tissue diagnosis is available in this case.

This case highlights the complexities of patient management in the acute setting after OLT. Furthermore, it demonstrates the intricate role of careful preoperative evaluation and screening in patients undergoing workup for solid organ transplantation. If one were to evaluate the cardiac and hepatic systems in series, the release of vasoactive peptides is a plausible explanation for masked pulmonary hypertension during the pre-transplant evaluation. Our patient had limited response to both medical and mechanical circulatory support, likely indicating her disease process was rapidly progressive.

As such, a combination of low PVR, high CO and normal PA pressures may be considered as a trigger to evaluate patients with serial post-transplant echocardiograms in order to assess for unmasked PoPHTN, especially in those developing ascites, dyspnea on exertion, or lower extremity edema with no other explanation. This hypothesis provides an opportunity for future study.

Pathophysiologic mechanisms for the development of acute or subacute moderate to severely elevated pulmonary hypertension in post OLT patients has been demonstrated and outlined above. Ongoing research into the fields of vasoactive signaling, pulmonary vascular remodeling, and BMPR2 are ongoing (18), and may shed some light into future therapies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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