Navigating a complicated liver transplant in a patient with severe hepatopulmonary syndrome without extracorporeal membrane oxygenation: a case report

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Singapore Med J 2022, 1–12
https://doi.org/10.11622/smedj.2022002
Published ahead of print: 27 January 2022

Online version can be found at
http://www.smj.org.sg/online-first
Dear Sir,

We herein report on a case of successful management of a liver transplant patient with significant hepatopulmonary syndrome (HPS). HPS is a hypoxaemic state that results from intrapulmonary vasodilation in patients with liver cirrhosis. Patients present with platypnoea and orthodeoxia secondary to ventilation-perfusion mismatches that worsen in the upright position but improve in the supine position,\(^1,2\) which is largely attributable to preferential perfusion of lung bases resulting in greater functional shunting in the upright position.\(^1\)

The prognosis of HPS is poor, with a five-year survival rate of 23\% and a median survival time of 24 months.\(^3\) A cohort study by Schenk et al showed that only 25% of patients with partial pressure of oxygen (\(\text{PaO}_2\)) level < 60 mmHg survived for six months.\(^4\) To date, medical management of patients with HPS includes nitric oxide antagonists, somatostatin analogues, cyclooxygenase inhibitors and immunosuppressive agents; however, the attendant mortality benefits have been marginal at best.\(^5\) Non-pharmacologic means of managing HPS by reduction of portal pressures using transjugular intrahepatic portosystemic shunts also failed to demonstrate significant benefits.\(^6\) Hence, orthotopic liver transplant is the definitive treatment for HPS.\(^7\) Nevertheless, post-transplant mortality remains high, with a one-year mortality rate of 29\% in patients with a shunt fraction of more than 20\% and \(\text{PaO}_2\) level of less than 50 mmHg.\(^8\)

Although HPS is expected to resolve within 6–12 months after transplantation in most cases,\(^9\) in the immediate postoperative phase, arterial oxygenation may worsen from pleural effusion, atelectasis or infections.\(^10\) Proposed mitigation measures include Trendelenburg positioning, inhaled epoprostenol, inhaled nitric oxide, intravenous methylene blue, embolisation of abnormal pulmonary vessels and extracorporeal membrane oxygenation.
Transplant centres have also reported that the survivability of post-liver transplant patients on ECMO support is nearly 50%, approximating that of non-transplant patients.

Herein, we would like to share about a patient who underwent a successful high-risk liver transplant and discuss the strategies that contributed to the good perioperative outcome. A 62-year-old man with well-controlled type 2 diabetes mellitus and hyperlipidaemia had been diagnosed with Child’s B9 liver cirrhosis secondary to non-alcoholic steatohepatitis. His condition was complicated by episodes of hepatic encephalopathy, mild ascites, portal hypertension, small oesophageal varices, portal gastropathy, hypersplenism and HPS. In addition, he was diagnosed with hepatocellular carcinoma of a 1.5-cm × 1.1-cm nodule in Segment 4 that was deemed unsuitable for radiofrequency ablation or transarterial chemo-embolisation.

On room air, the patient’s PaO$_2$ level was 42.5 mmHg, and he required long-term oxygen therapy at 2 L/min. A cardiac bubble study showed a left ventricular ejection fraction of 68%, pulmonary arterial pressure of 26 mmHg and significant pulmonary arteriovenous shunting, evidenced by visibility of bubbles in the left heart after four cardiac cycles. A technetium-99 isotope study quantified a shunt fraction of 39%, with significant extrapulmonary deposition of macroaggregated albumin in the brain, spleen and kidneys.

Although the Model for End-stage Liver Disease score of the patient was 16, he was prioritised for an elective deceased donor liver transplant in view of his severe hepatopulmonary syndrome. Once a potential suitable donor liver was identified, the transplant team facilitated an immediate preoperative workup. An institutional workflow was in place for referrals to the in-house cardiothoracic surgeon for possible ECMO. The workflow also involved interventional radiology-guided central venous catheter (CVC) placement by the interventional radiologist one hour prior to surgery. The patient had a CVC and swan sheath catheter inserted in the left internal jugular vein, as well as Certofix® 16-G cannulas inserted
in the right internal jugular vein and the right common femoral vein for immediate implementation of ECMO if required, to avoid any possibility of cerebral hypoperfusion (Fig. 1).

The patient underwent a nine-hour-long allograft transplant with a anhepatic phase of 133 minutes, a cold ischaemic time of 315 minutes and a warm ischaemic time of 67 minutes. A side-to-side cavo-cavostomy was performed with an end-to-end recipient portal vein to donor portal vein. An end-to-end biliary anastomoses was also performed.

The patient was kept on a fentanyl and atracurium infusion for the surgery. A FloTrac device was used to guide intraoperative fluid and inotrope therapy in accordance with his stroke volume variation, cardiac index, systemic vascular resistance and systemic vascular resistance index. In addition, a cardiologist was available to perform serial trans-oesophageal echocardiography examinations during the post-induction, anhepatic phase, immediately before reperfusion and during reperfusion of the liver.

In view of the patient’s severe pulmonary hypertension, additional measures were taken to ensure adequate oxygen delivery by addressing each component of the oxygen flux equation. Blood transfusion was performed expediently, with perfusion pressure and cardiac output maintained with inotropes, as required. Cerebral oximetry was monitored, and decreases in oximetry were treated effectively with titrated fraction of inspired oxygen (FiO₂) requirements to keep his oxygen saturation (SpO₂) level above 95%. This higher limit was necessary so that there would be a buffer against anticipated blood loss, fluid shifts and hemodynamic changes that affect oxygen flux. Other indicators of adequate oxygenation, such as lactate and mixed venous oxygen saturation (SvO₂), were also monitored.

During the surgery, the patient required noradrenaline, adrenaline and vasopressin infusions. Owing to an estimated blood loss of 3.6 L, the patient was provided 5 L of 5% albumin, 1.5 L of plasmaLyte, 2,198 mL of packed red blood cells, 2,468 mL of fresh frozen
plasma, 649 mL of pooled platelets and 4 g of fibrinogen concentrate, with the transfusion strategy guided by rotational thromboelastometry.

After the surgery, the patient was kept intubated and transferred to the surgical intensive care unit (SICU). The transplant team started with stratified immunosuppressive therapy with hydrocortisone, mycophenolate and tacrolimus in accordance with the institutional protocol. Doppler ultrasonography of the liver on postoperative day (POD) 1 showed patent inflow and outflow vessels with good resistive indices. The patient was restarted on trophic feeds through his nasogastric tube. Liver enzymes were monitored twice a day, until a downward trend of bilirubin and transaminases was noted on POD 4.

Postoperatively, the patient’s ECMO lines were kept in anticipation of possible worsening of HPS or complications from transfusion-related acute lung injury or fluid overload. However, the patient was able to maintain a PaO₂ level of more than 60 mmHg on FiO₂ of 40%, and hence the intensive care unit (ICU) team decided for early extubation on POD 2. However, shortly after extubation, the patient was found to be dyspnoeic with increasing drowsiness, corresponding to an SpO₂ level of 81% and a PaO₂ level of 54.2 mmHg despite being on a Venturi mask delivering an FiO₂ level of 50%. This was treated promptly with a high-flow nasal cannula (HFNC) and diuresis with furosemide, with the working diagnosis of a Type 1 respiratory failure secondary to pulmonary congestion (Table I).

Over the next two days, the patient continued to require HFNC, with an FiO₂ level of up to 60% despite achieving adequate diuresis, administration of mucolytic agents and aggressive chest physiotherapy. On POD 4, the nurses and the physiotherapist noted a pattern of desaturation whenever the patient was made to sit on a chair, which promptly resolved when the patient was laid supine. The ICU team then concluded that the patient’s persistent hypoxaemia was attributable to unresolved HPS and started weaning oxygen requirements
when the patient was supine, while judiciously tolerating desaturation levels of up to 80% when he was upright and undergoing ambulatory physiotherapy.

The transplant team was also apprised of the persistent HPS, as they had concerns about graft failure from hypoxaemia. However, the patient’s liver function tests and ultrasonography investigations indicated improving graft function, and his lactate levels remained within the normal range. Hence, with a good graft arterial and portal venous flow, surgeons were confident of graft viability and were able to accept a lower systemic PaO$_2$ level, knowing that the oxygen supply would be adequate.

By POD 5, the patient was discharged to the high-dependency unit (HDU) on a HFNC of 40 L/min, with an FiO$_2$ level of 45%. The ECMO lines were removed prior to transfer, with no complications observed throughout the procedure. While under close observation in the HDU, the patient was weaned off HFNC to nasal prongs on POD 7 and sent to the general ward. Subsequently, the patient still required 3 L/min of oxygen prior to discharge, which was his baseline. This was weaned off one month after discharge (PaO$_2$ 73 mmHg on room air), and at one year, the patient was saturating well without supplementary oxygen. No long-term transplant-related complications were detected.

<p>| Table I. Arterial blood gas (ABG) readings before transplant, in the hospital and upon discharge. |</p>
<table>
<thead>
<tr>
<th>Reading</th>
<th>FiO2</th>
<th>pH</th>
<th>PaO2 (mmHg)</th>
<th>PaCO2 (mmHg)</th>
<th>Base excess</th>
<th>HCO3 (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.21</td>
<td>7.42</td>
<td>42.5</td>
<td>35.0</td>
<td>−1.7</td>
<td>22.9</td>
</tr>
<tr>
<td>On long-term oxygen therapy</td>
<td>0.36</td>
<td>7.47</td>
<td>71.6</td>
<td>31.6</td>
<td>−0.4</td>
<td>24.0</td>
</tr>
<tr>
<td>Post-transplant in ICU (POD 1)</td>
<td>0.40</td>
<td>7.46</td>
<td>62.7</td>
<td>37.0</td>
<td>3.0</td>
<td>26.9</td>
</tr>
<tr>
<td>1 hour after extubation in ICU (POD 2)</td>
<td>0.50</td>
<td>7.49</td>
<td>54.2</td>
<td>33.8</td>
<td>2.2</td>
<td>26.2</td>
</tr>
<tr>
<td>High-flow nasal cannula (POD 2)</td>
<td>0.50</td>
<td>7.50</td>
<td>58.0</td>
<td>32.7</td>
<td>1.6</td>
<td>25.7</td>
</tr>
<tr>
<td>High-flow nasal cannula (POD 3)</td>
<td>0.60</td>
<td>7.50</td>
<td>50.2</td>
<td>33.1</td>
<td>2.3</td>
<td>26.3</td>
</tr>
</tbody>
</table>
Previously, patients with liver failure, high HPS shunt fraction and arterial hypoxaemia < 50 mmHg were excluded from transplantation because they were considered as having severe cardiopulmonary disease.\(^{(13)}\) However, with advances in medical technology and procedural expertise, these patients have been recently included as transplant candidates.

Reports of patients with severe HPS undergoing successful liver transplantation are scarce, and there are few reported cases on the use of postoperative ECMO. Sharma et al\(^{(12)}\) have reported the use of postoperative ECMO in a 60-year-old woman with HPS and a PaO\(_2\) of 50 mmHg who had undergone a liver transplant. Kumar et al\(^{(14)}\) have also reported a case of a 16-year-old boy with HPS and a PaO\(_2\) of 37 mmHg who underwent a successful living-related donor transplant but subsequently developed desaturation on POD 2, which was attributable to worsening HPS, finally requiring salvage ECMO. In our case, we adopted an approach to enhance the perioperative oxygen delivery of the patient by applying the principles of the following oxygen flux equation, especially at significant points of clinical decision-making:

\[
\text{Flux} = \left(\text{Cardiac output} \times \text{Haemoglobin concentration} \times \text{Saturation} \times \text{Huffner's constant}\right) + (0.003 \times \text{PaO}_2).
\]

Perioperatively, surrogate markers of aerobic and anaerobic respiration such as lactate levels and SvO\(_2\) were also monitored to ensure adequate oxygen delivery. The fact that these values remained in their expected range (with lactate reaching a peak of 4.5 mmol/L during reperfusion, trending down to 0.97 mmol/L at the end of surgery and remaining in the normal
range postoperatively) suggested that oxygen delivery to the rest of the body was sufficient despite the borderline PaO$_2$. This underpins the importance of managing each patient according to their unique pathophysiological status and tailoring respective management strategies according to their specific needs.

Table II. Significant events that occurred intraoperatively and during the immediate postoperative period.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intraoperative</th>
<th>POD 2</th>
<th>POD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>O$_2$/ventilator requirement</td>
<td>Volume-controlled ventilation PEEP: 5, Tidal Vol (mL): 500, I:E ratio: 1:2, Rate: 12</td>
<td>Continuous positive airway pressure PEEP: 5 FiO$_2$: 0.40</td>
<td>Venturi mask FiO$_2$: 0.50</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Within normal range</td>
<td>Not monitored but haemodynamically stable without inotropic support, patient clinically well</td>
<td>Day of extubation</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>6.8 (blood transfusion ongoing)</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>SaO$_2$ (%)</td>
<td>100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>PaO$_2$ (mmHg)</td>
<td>94</td>
<td>95.4</td>
<td>51</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>4.5</td>
<td>0.7</td>
<td>0</td>
</tr>
</tbody>
</table>

FiO$_2$: fraction of inspired oxygen; Hb: haemoglobin; I:E ratio: inspiratory to expiratory ratio; O$_2$: oxygen; PaO$_2$: partial pressure of oxygen; PEEP: positive end-expiratory pressure; POD: postoperative day; SaO$_2$: arterial oxygen saturation

As HPS leads to a decrease in SaO$_2$ and PaO$_2$, veno-venous ECMO could be used to address this. After due deliberation of the risk-benefit ratio, our patient was primed for ECMO because of severe pre-transplant arterial hypoaemia. A multidisciplinary approach involving cardiothoracic surgeons, perfusionists and an interventional radiologist was adopted, with a
clear protocol on when ECMO would be initiated if hypoxaemia became significant. We sought to minimise the risks of pre-emptive ECMO line insertion by inserting them percutaneously under fluoroscopic guidance. To mitigate the possible use of ECMO, other variables of the equation were optimised to sustain adequate oxygen delivery to vital organs, including the grafted liver. The anaesthetists optimised the haemoglobin level to around 8 g/dL considering the impact of optimal rheology and titrated the FiO\textsubscript{2} up to 80% to keep saturation > 88%. In addition, inotropic support was started pre-emptively to mitigate possible decreases in cardiac output from vasodilation or surgical haemorrhage. Due consideration was given to induced hypothermia to reduce tissue metabolism, but this was not initiated owing to inherent risks of exacerbating coagulopathy in a patient who already has clotting factor deficits.

Despite the persistence of postoperative hypoxaemia, postoperative ultrasonography showed a healthy graft with good arterial and portal venous flow. Hence, with the confidence that the cardiac output and haemoglobin levels were able to compensate for the decreased haemoglobin saturation, the SICU team decided to extubate the patient and commence weaning of his oxygen therapy.

Liver transplant recipients with HPS of high shunt fraction can be managed without ECMO in the intraoperative and postoperative setting. Such patients do not necessarily require prolonged intubation for persistent hypoxaemia. However, achievement of this outcome would require addressing multiple components of oxygen delivery, while still bearing in mind the potential need to start ECMO should initial interventions prove insufficient. As such situations are infrequent yet require the need for timely management, having a protocol with the rescue measures, cut-offs and workflow for the management of severe HPS in liver transplant helps to ensure expedient patient management in a clear and consistent manner.

In our case, we believe that the avoidance of ECMO and early extubation were attributed to the pre-emptive transfusion strategies to maintain a reasonable haemoglobin level,
coupled with the maintenance of oxygen flux and delivery by ensuring stable perioperative haemodynamics. In addition, maintenance of oxygen flux contributed to preservation of graft function and survival, and the patient was back in the community without oxygen therapy at the time of writing this study. We believe that the successful management of this patient was attributable to a collaborative, integrative and interdisciplinary multi-professional approach, right from the time when the patient was discussed as a potential candidate for liver transplant.

We would also like to acknowledge the following individuals for their contributions in this case: Dr Boey Sek Koon, Senior Consultant, Division of Anaesthesiology and Perioperative Medicine, Singapore General Hospital; Dr Ng Shin Yi, Head and Senior Consultant, Department of Surgical Intensive Care, Division of Anaesthesiology and Perioperative Medicine, Singapore General Hospital; A/Prof Ong Gek Khim Sharon, Senior Consultant, Department of Surgical Intensive Care, Division of Anaesthesiology and Perioperative Medicine, Singapore General Hospital; Dr Chee Huei Leng, Senior Consultant, Department of Surgical Intensive Care, Division of Anaesthesiology and Perioperative Medicine, Singapore General Hospital; and Adj A/Prof Prema Raj Jeyaraj, Department of Hepato-pancreatic-biliary and Transplant Surgery, Singapore General Hospital, SingHealth Transplant, National Liver Transplant Programme, Singapore.

Yours sincerely,

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REFERENCES


FIGURE

**Activation of deceased-donor liver transplant patient in the ward**

Potential need for intraoperative VV ECMO is high

To Intervventional Radiology for pre-ECMO lines insertion. Additional lines upon anaesthetist's request.

Potential need for intraoperative VV ECMO is low

To operating theatre

To keep right IJV and both femoral veins available for access if needed.

To operating theatre

**Yes**

CTS and perfusionist called back

Plan A: ECMO tubing insertion via pre-ECMO lines (by IR) using Seldinger's technique and confirmed by portable image intensifier (II) machine or TEE.

or

Plan B: ECMO tubing insertion without pre-ECMO line using open technique or ultrasonography guidance.** (Anaesthetist/IR may offer help if needed) ECMO initiated by perfusionist. (Heparin given by anaesthetist before initiation.)

**No**

Transplant surgery completed

To surgical intensive care unit

*Fig. 1* Flowchart shows proposed strategy for perioperative management of severe hepatopulmonary syndrome undergoing liver transplant.

*Severe persistent hypoxaemia: SpO₂ 85% or below patient's normal (pre-induction) PaO₂ values despite FiO₂ of 100% with a PEEP of > 10 mmHg, and which is out of proportion to any other concurrent lung processes. CTS: cardiothoracic surgeon; FiO₂: fraction of inspired oxygen; ECMO: extracorporeal membrane oxygenation; IJV: internal jugular vein; IR: interventional radiology; TEE: trans-esophageal echocardiography; VV ECMO: veno-venous extracorporeal membrane oxygenation*