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Combined lung and liver transplantation in a girl with cystic fibrosis

Purpose: To describe the anesthetic considerations of a combined lung and liver transplant in a 14-yr-old girl with cystic fibrosis.

Clinical features: A 14 yr-old girl with cystic fibrosis presented for combined liver and lung transplantation. Anesthetic management was complex in that the pulmonary, hemodynamic, and hematological changes after cardiopulmonary bypass and lung transplantation made the management of the subsequent liver transplant unique. We used a moderate dose fentanyl and isoflurane anesthetic with invasive monitoring including a pulmonary artery catheter. Upon reperfusion of the new liver our patient exhibited severe pulmonary hypertension that was associated with a decrease in cardiac output and systemic hypotension. Utilizing a pulmonary artery catheter, this episode was treated with an increase of prostaglandin E₁ (PGE₁) infusion to 0.025 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and the initiation of 3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dobutamine. The pulmonary hypertension resolved and the cardiac output and blood pressure returned to baseline levels.

Conclusion: The anesthetic considerations for a combined lung and liver transplant are complex because of the interactions and alterations in cardiovascular, pulmonary and hemostatic systems. The use of a pulmonary artery catheter was critical to the management of our patient because it allowed us to accurately treat an episode of hypotension occurring during liver transplantation. This episode was secondary to acute pulmonary hypertension which is common after pulmonary transplantation but unusual during liver transplantation. It is also critical that a team approach is used to consider all of the concerns of the multiple services managing these complex patients.

Objectif : Décrire les composantes anesthésiques d'une greffe combinée du poumon et du foie chez une jeune fille de 14 ans atteinte de fibrose kystique.

Éléments cliniques : Une jeune fille de 14 ans atteinte de fibrose kystique devait subir une greffe combinée du foie et du poumon. L'anesthésie a été complexe, car les changements pulmonaires, hémodynamiques et hématologiques causés par la circulation extracorporelle et la transplantation du poumon ont influencé de façon unique la greffe du foie qui a suivi. On a utilisé une dose modérée de fentanyl et d'isoflurane et un monitoring effractif comprenant un cathéter de l'artère pulmonaire. À la reperfusion du nouveau foie, on a noté une hypertension pulmonaire sévère associée à une baisse du débit cardiaque et à une hypotension générale. Cet épisode a été traité avec une perfusion accrue de prostaglandine E₁ (PGE₁) jusqu'à 0,025 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ et l'administration de 3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ de dobutamine à l'aide du cathéter de l'artère pulmonaire. L'hypertension pulmonaire s'est résorbée et le débit cardiaque ainsi que la tension artérielle sont revenus à la normale.

Conclusion : La greffe combinée du poumon et du foie demande un aménagement anesthésique complexe à cause des changements cardio-vasculaire, pulmonaire et hémostatique et aux interactions entre ces systèmes. L'usage d'un cathéter de l'artère pulmonaire a été décisif, puisqu'il nous a permis de traiter efficacement l'hypotension survenue pendant la greffe du foie. Cet épisode était secondaire à l'hypertension pulmonaire aiguë, fréquente à la suite d'une greffe pulmonaire mais inhabituelle pendant la greffe du foie. Dans des situations cliniques d'une telle complexité, il est crucial de travailler en équipe afin de tenir compte de toutes les composantes des multiples services nécessaires.

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CYSTIC fibrosis (CF) is an autosomal recessive disorder characterized by exocrine gland dysfunction resulting in severe chronic pulmonary disease, pancreatic dysfunction, and hepatic dysfunction. Recently, combined lung and liver transplantation has been advocated for CF patients with end-stage lung and hepatic disease.¹ To date there is little information describing anesthetic considerations for this combined procedure.² Both lung and liver transplantation, when performed separately are associated with multiple alterations in the cardiovascular, pulmonary, and hemostatic systems. We describe the case of a 14-year-old CF patient with end-stage liver and lung disease presenting for combined organ transplantation.

Case report

The patient is a 14 yr-old girl, 40 kg, ASA physical status IV, with cystic fibrosis, who presented for combined lung and liver transplantation. She presented 12 days before transplantation with deteriorating respiratory function requiring tracheal intubation. Her past medical history included CF associated with severe end stage obstructive lung disease requiring lobectomy for pneumonia at nine years (FEV_1 , 18% of predicted value). She also had severe end stage liver disease secondary to focal biliary cirrhosis associated with portal hypertension, intermittent hepatic encephalopathy, and multiple episodes of bleeding esophageal varices. These numerous episodes of bleeding required multiple surgical procedures including, banding, sclerosis, coil embolization, and four different diverting shunts. She had no known drug allergies and was receiving multiple medications including, neomycin, spironolactone, ciprofloxacin, famotidine, ursodiol, nadolol, and vitamin K.

On the day of the transplant, the patient was awake but anxious. The trachea had been intubated two days before the procedure secondary to tachypnea and hypoxia and she was breathing oxygen 30% with a PaO_2 of 90 mmHg, $PaCO_2$ 53 mmHg, and a pH of 7.37. Other laboratory values included: hemoglobin (Hgb) 10.7 mg-dl⁻¹, hematocrit 33.2%, platelet count 166 k-mm⁻³, protime 13.1 sec, partial thromboplastin time 37.1 sec, total bilirubin 15.5 mg-dl⁻¹, SGOT 280 iu-l⁻¹, SGPT 91 iu-l⁻¹. Intravenous access included a 7 French double lumen central venous catheter in the left external jugular vein. She was brought to the operating room after sedation with 3 mg midazolam *iv* titrated over 10 min. After placement of routine monitors (blood pressure cuff, pulse oximeter and electrocardiogram), anesthesia was induced with 2 mg midazolam, and 20 µg-kg⁻¹ fentanyl titrated over 10

min. Neuromuscular blockade was achieved with 4 mg pancuronium bromide. After induction of anesthesia, two 14 g peripheral intravenous lines were placed, a 7 FR introducer was placed in the right internal jugular vein, and a 5.5 FR oximetric pulmonary artery catheter was inserted. Due to the eventual resection of both pulmonary arteries, the pulmonary artery catheter was floated only to the central venous position at 15 cm. Antifibrinolytic therapy was initiated with a loading dose of 240 mg·m⁻² aprotinin followed by a continuous infusion of 56 mg·m⁻²·hr⁻¹. Anesthesia was maintained with isoflurane 0.3 to 0.5% inspired in an air/oxygen mixture and supplemental doses of fentanyl and midazolam. Volume control ventilation was delivered via the anesthesia machine (Seimens 900C) and adjusted to arterial blood gas measurements.

The initial surgical procedure was bilateral sequential lung transplant via a bilateral anterior transsternal thoracotomy incision. The hemodynamic and laboratory data are presented in Table. The patient was anticoagulated with 12,000 u heparin and was placed on cardiopulmonary bypass (CPB) via right atrial and aortic cannulae. The CPB pump was primed with crystalloid and one unit of packed red cells (PRBCs) was added because the initial hemoglobin concentration on CPB was 5.9 mg-dl⁻¹. Both lungs were resected and the donor lungs were sequentially transplanted in the left and right chest. Prior to unclamping the pulmonary arteries, an infusion of 0.0125 µg·kg⁻¹·min⁻¹ prostaglandin E₁ (PGE₁) was administered to prevent reperfusion injury and for its dilating effect on the pulmonary vascular resistance.^{3,4} The pulmonary artery catheter was then floated into the right pulmonary artery. The patient was weaned off CPB and required inotropic support with 7.5 µg·kg⁻¹·min⁻¹ dopamine. A technique of modified ultrafiltration was used to remove 1800 ml fluid resulting in a Hb of 10.1 mg-dl⁻¹. The heparin was reversed with protamine. After adequate hemostasis was achieved, the chest was packed and left open in case exploration was needed during the liver transplant. The duration of the lung transplant was six hours and 30 min.

Prior to the liver transplant, the Hb was 7.3mg-dl⁻¹, platelets 89,000/·cmm⁻¹, PT 17.8 sec, and PTT 102.5 sec. She was transfused with two units PRBCs and two units fresh frozen plasma (FFP). During the liver transplantation, arterial, central venous, and pulmonary artery pressures were measured as well as cardiac output and mixed venous oxygen saturations. Complete blood counts (CBCs), arterial blood gases (ABGs), and coagulation parameters were performed hourly and blood product administration was based on laboratory data

TABLE

	Baseline/Preop	Post induction	post CPB	Liver TX1 hour (Prehepatic)	Liver TX2 hour (Begin Anhepatic)	Liver TX3 hours (Anhepatic)	Liver TX4 hours (Posthepatic)	Liver TX6 hours (Post Hepatic)	End of Liver TX
<i>Hemodynamics</i>									
Blood pressure mmHg	84/40	87/42	80/42	79/42	75/45	55/30	65/37	85/40	84/42
Heart Rate bpm	95	84	105	115	120	115	110	120	112
CVP mmHg			11	11	11	15	15	14	18
PA mmHg				42/21	44/28	55/28	41/29	46/24	38/22
CO L·min ⁻¹			5.6	5.2	5.3	3.6	5.1	5.4	5.2
Temperature °C	37	35.7	36.5	36.8	37.1	37.2	36.3	36.6	36
<i>Respiratory</i>									
FiO ₂	0.3	1	1	1	1	1	1	1	1
SaO ₂	97	100	100	100	100	100	100	100	100
pH	7.42	7.31	7.41	7.43	7.48	7.38	7.29	7.48	7.58
PCO ₂ mmHg	38	64	37	37	30	37	38	32	31
PO ₂ mmHg	73	329	435	255	429	139	165	185	518
<i>Laboratory</i>									
Hgb mg·dl ⁻¹	10.7	10.5	7.3	9.3	12.8	9.7	10.3	10.3	8.2
Platelets (x 1000)	166		89	70	68	96	50	74	38
PT sec	13.1		17.8	14.4	14.8	13.1	14.1	13.7	15
PTT sec	37.1		102.5	91.5	116	91.6	>120	110	>120
Fibrinogen mg·dl ⁻¹			105	132	125	132	111	153	121
<i>Interventions</i>									
			PRBCs and FFP Begun Dopamine and PGE ₁ started	FFP and PRBCs continued	FFP Continued, platelets begun	PGEI increased, dobutamine started, FFP continued	Platelets and FFP continued, cyroprecipitate started, Dopamine increased, Dobutamine added.	FFP weaned off. Dopamine weaned to 7.5 µg·kg ⁻¹ ·min ⁻¹	Platelets FFP and PRBC's given. Chest explored, blood evacuat- ed, and closed. TO ICU

and clinical bleeding. Three hours after the start of the liver transplant, the patient became hypotensive. This was precipitated by an increase in PA pressure from 41 to 55 mmHg (systolic) and an associated decrease in cardiac output (5.3 L·min⁻¹ to 3.6 L·min⁻¹). Changes also occurred in MVO₂ (78% to 66%), PaO₂ (236 mmHg to 139 mmHg), PCO₂ (32 mmHg to 38 mmHg), pH (7.44 to 7.29) and an increase in CVP (11 mmHg to 16 mmHg). This episode occurred about ten minutes after the reperfusion of the new liver. Dobutamine was instituted at 3 µg·kg⁻¹·min⁻¹ and the PGE₁ infusion was doubled to 0.025 µg·kg⁻¹·min⁻¹. Subsequently the blood pressure improved and the PA pressures decreased to 36 mmHg (systolic). This episode was attributed to the acidosis associated with reperfusion of the new liver. The dobutamine was subsequently weaned over three hours and the PGE₁ was decreased to the pre liver transplant rate (0.0125 µg·kg⁻¹·min⁻¹). At the end of liver transplantation, PaO₂

decreased to 76 mmHg without any associated hemodynamic changes, so the chest was explored. A large collection of blood was evacuated and bleeding sites were cauterized. This allowed greater expansion of the lungs and the PaO₂ increased to 518 mmHg. The chest was then closed. During the entire procedure the patient received a total of eight units PRBCs, eight units FFP, six units platelets, and one unit cryoprecipitate, three litres of crystalloid and 750 ml albumin 5%. The aprotinin was discontinued at the end of the procedure, and she was transported to the pediatric intensive care unit receiving 7.5 µg·kg⁻¹·min⁻¹ dopamine and 0.0125 µg·kg⁻¹·min⁻¹ PGE₁. The total anesthesia time was 18 hr. Her post-operative course was complicated by an increase in chest tube output that required re-exploration on the first postoperative day where a bleeding site was cauterized. The trachea was extubated on the third postoperative day, and she was discharged on the 18th postoperative day.

Discussion

Multiple organ transplantation is the only therapeutic option for some patients with systemic diseases affecting multiple organ systems. We describe the successful management of a 14 yr-old girl with cystic fibrosis who underwent combined lung and liver transplantation using a moderate dose opioid and isoflurane technique, aprotinin and a pulmonary artery catheter.

From a hemodynamic perspective, we placed a pulmonary artery (PA) catheter even though they are not routinely used in pediatric patients undergoing lung transplantation. We felt that monitoring cardiac output and PA pressures would be critical because pulmonary hypertension and graft dysfunction can occur in the early postoperative period especially after the use of cardiopulmonary bypass.⁵ Liver transplantation is often associated with hypotension but this is usually a result of hypovolemia, bleeding and a decrease in filling pressures. Hypotension can also be associated with venous air embolus. It would be difficult to assess hemodynamic changes accurately during liver transplantation after the use of cardiopulmonary bypass and lung transplantation without a method of measuring cardiac output and pulmonary artery pressures. The use of transesophageal echocardiography would be useful in differentiating hemodynamic changes, but is contraindicated in patients with esophageal varices. Our patient exhibited an episode of hypotension during liver transplantation which was precipitated by an episode of pulmonary hypertension. Pulmonary hypertension with an associated decrease in CO and systemic blood pressure is not uncommon after lung transplantation, but is not a typical cause of hypotension during liver transplantation. This episode was responsive to an increase in PGE₁ and the addition of dobutamine.

In this case, as in most of our pediatric lung transplants, we used a combination of a moderate dose narcotic technique with low dose isoflurane. This anesthetic technique is also commonly used in liver transplants. The use of moderate doses of fentanyl has been shown to blunt the stress response in children with congenital heart disease and has also been shown to blunt the pulmonary vascular response to airway manipulation.⁶⁻⁸ Although blunting pulmonary vascular reactivity to the stress response and airway manipulation is critical during lung transplantation, there are no reports specifically examining this in the literature. Additionally, we used pancuronium bromide for neuromuscular blockade because we specifically wanted a muscle relaxant that had no histamine response and postoperative ventilation was anticipated. Nitrous oxide was avoided to prevent potential bowel distension.

Nitrous oxide can also increase the size of air emboli that have been associated with liver transplantation as well as with cardiopulmonary bypass.

An unusual aspect of this combined transplant was the management of hemostasis. At our institution, pediatric lung transplantation is always facilitated with the use of cardiopulmonary bypass. In the adult population, one lung ventilation without cardiopulmonary bypass is often the preferred technique. Liver transplantation alone is associated with severe coagulopathies including factor deficiencies and massive transfusion, but when the use of cardiopulmonary bypass is used prior to the procedure, marked changes were anticipated. A dilutional coagulopathy and thrombocytopenia secondary to cardiopulmonary bypass only exacerbates the hemostatic alterations associated with hepatic failure and liver transplantation. Our patient had moderate thrombocytopenia as well as a dilutional coagulopathy at the end of the lung transplantation which required factor replacement prior to the start of the liver transplant. We also monitored CBCs, PT, PTT, and fibrinogen hourly and tailored additional transfusion based on abnormal laboratory values and clinical bleeding. During the entire procedure the patient received eight units PRBCs, eight units FFP, six units platelets and one unit of cryoprecipitate.

Several studies have shown a considerable decrease in blood loss during lung transplantation with the use of aprotinin.⁹⁻¹¹ At our institution, we routinely use the antifibrinolytic agent aprotinin for pediatric lung transplantation. Antifibrinolytic agents have been implicated in hepatic vein thrombosis and their use in liver transplantation is controversial.² After discussions with both surgical teams, we elected to use aprotinin because of the increased risk of bleeding with the combined procedures.

We have described the successful management of a 14 yr-old girl who underwent a combined liver and lung transplant. The anesthetic management for these patients should take into account the interactions and alterations in cardiovascular, pulmonary and hemostatic systems. In our case we have shown how a pulmonary artery contributed to the successful outcome. Our patient's episode of hypotension during the liver transplantation was not secondary to hypovolemia but secondary to an episode of pulmonary hypertension. It is also critical that a team approach is used to consider all of the concerns of the multiple services managing these complex patients.

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