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Case Report

Alagille Syndrome and Repeat Oxygenator Failure during Cardiopulmonary Bypass: A Word of Caution

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Abstract: Alagille syndrome is an autosomal dominant disorder that is caused by heterozygous mutation of JAG1 or NOTCH2 gene that impacts several multisystem organs including but may not be limited to the liver, heart, musculoskeletal, skin, and the eyes. The most common congenital heart defect associated with Alagille syndrome is multilevel right ventricular outflow tract obstruction with multiple central and peripheral branch pulmonary arterial stenoses occurring in up to two-thirds of these patients. We report two cases of Alagille syndrome who underwent extensive pulmonary arterial branch rehabilitation and experienced unusual oxygenator failure during cardiopulmonary bypass (CPB). We present lessons learned from these two cases and the changes that we implemented in our practice that facilitated smooth conduct of CPB in other cases that we performed subsequently. **Keywords:** Alagille syndrome, pulmonary arterioplasty, pulmonary artery reconstruction, oxygenator failure. *J Extra Corpor Technol. 2022;54:338–42*

Alagille syndrome is an autosomal dominant disorder that is caused by a heterozygous mutation of JAG1 or NOTCH2 gene which amounts to a complex multisystem disorder occurring 1 in 70,000 births (1,2). The body systems that are primarily involved are the liver, heart, skeleton, face, and eyes. The majority of Alagille's syndrome patients have liver disease, with up to 95% present with chronic cholestasis generally caused by the paucity of intrahepatic bile ducts. The patients most commonly present in the first 3 months of life with jaundice from conjugated hyperbilirubinemia (2). Liver disease progressing to cirrhosis and failure may lead to transplantation in 15% of patients (3).

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More than 90% of these patients present with cardiac anomalies (4), and the most common congenital heart defects usually involve the right ventricular outflow tract (RVOT), with peripheral and central branch pulmonary arterial stenoses occurring in up to 60%. Tetralogy of Fallot (TOF) occurs in up to 16% of patients (2–4). The most common etiology behind the early mortality in these patients is congenital heart disease, while the one behind late mortality is liver failure (2). The complexity of these cardiac defects requires complex surgical pulmonary arterial reconstructions to improve the right ventricular pressures. These procedures usually require extensive pulmonary arterial branch plasties with or without repair of associated cardiac defects (5). The operations typically are long and require long cardiopulmonary bypass (CPB) runs.

Failure of the oxygenator during CPB is rare, but can be problematic especially if occurred during the critical portion of the procedure. Fortunately, these failures are not that frequent and can be troubleshooted if they occur. In 2010, 101 failures were reported, and in 2011 only 103 failures were reported to the manufacturer and user's device experience website in the United States (6). Several etiologies may contribute to oxygenator failure such as inadequate anticoagulation, and long CPB runs which may be required

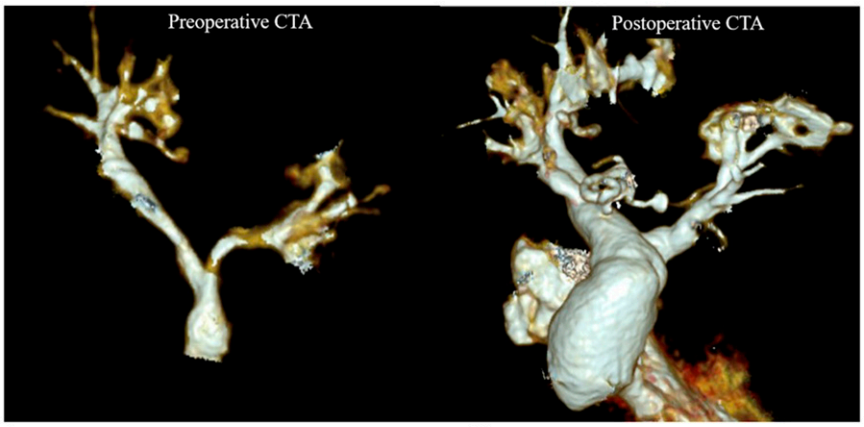

Figure 1. Branch pulmonary arteries as shown by 3D reconstruction of the computed tomographic (CT) scan (A) preoperatively and (B) after reconstruction.

in some of the complex cardiac cases and where extensive pulmonary arterial reconstruction is needed as in Alagille's syndrome and unifocalization procedures.

A case report by Badulak et al. demonstrated an oxygenator failure due to hypertriglyceridemia in a patient who was supported with veno-venous extracorporeal membrane oxygenation (ECMO) (7). To the authors' knowledge, there is no published studies of oxygenator failure in Alagille's syndrome. In this cases report, we are discussing two patients with Alagille syndrome undergoing complex cardiac reconstructions on CPB in which repeated oxygenator failures occurred.

CASE 1

Diagnosis and Preoperative Work-up

An 8.8 kg, 7-month-old infant was diagnosed with TOF and Alagille syndrome. Preoperative imaging showed typical features of TOF with hypoplastic main and bilateral branch pulmonary arteries (PAs) (Figure 1A). This patient had hyperbilirubinemia, vitamin D deficiency, and cholestasis. Preoperative laboratory work up is shown in Table 1.

Table 1. Preoperative laboratory work-up in both cases.

Laboratory Test/Normal Values	Case 1	Case 2
Total bilirubin (0.2–1.3 mg/dL)	11.7 mg/dL	8.6 mg/dL
Direct bilirubin (0–0.2 mg/dL)	9.4 mg/dL	7.7 mg/dL
GGT (0–30 Units/L)	777 Units/L	2,360 Units/L
ALT (0–50 Units/L)	457 Units/L	215 Units/L
AST (20–65 Units/L)	31 Units/L	161 Units/L
Alkaline phosphatase (110–320 Units/L)	577 Units/L	852 Units/L
Ferritin (7–142 ng/mL)	786 ng/mL	274 ng/mL
Fibrinogen (200–420 mg/dL)	446 mg/dL	134 mg/dL
Cholesterol (<170 mg/dL)		525 mg/dL
HDL (≥50 mg/dL)		13 mg/dL
LDL (<110 mg/dL)		464 mg/dL
Triglycerides (<75 mg/dL)		238 mg/dL

GGT, gamma glutamyl transferase; ALT, alanine transaminase; AST, aspartate transaminase; HDL, high density lipoprotein; LDL, low density lipoprotein.

Cardiopulmonary Bypass Circuit Set-up

CPB equipments used included a 3/16-1/4 AV loop, FX05 oxygenator (Medtronic, Minneapolis, MN), CDI 500 (Terumo, Somerset, NJ), bio-console 560 arterial line flow probe (Medtronic), and HMS plus (Medtronic). CPB circuit was primed with 600 mL of plasmalyte, 4.5 mg mannitol, 15 mEq sodium bicarbonate, 135 mg of Solu Medrol, 2,000 units of heparin, 250 mL of 5% albumin, 200 mg Cefazolin, 35.1 mg Tranexamic Acid (TXA). Total of 350 mL of red blood cells (RBCs) were given during CPB.

Conduct of the Procedure

The procedure was performed via a standard median sternotomy. Prior to heparinization, extensive bilateral mobilization of the PA and its branches down to the lobar and segmental ones were performed. Heparin was then administered systemically (400 Units/kg) and the proximal aortic arch was cannulated using a 10 Fr DLP arterial cannula and the right atrial appendage was cannulated with an 18-Fr straight single stage venous cannula. Initial Activated clotting time (ACT) was >999 seconds (Heparin dose response: 1.3 mg/kg) and CPB was initiated without difficulty and core temperature was brought down to 32°C. The surgeon performed bilateral branch pulmonary arterioplasties first on beating heart and then proceeded with TOF repair in the standard fashion. The single stage venous cannula was switched to bicaval using a 14-Fr and 16-Fr right angled metal tipped and the heart was arrested with 30 mL/kg of del Nido solution in an antegrade fashion. The repair involved transatrial closure of the ventricular septal defect, and transannular patch, leaving a small atrial level shunt. This was done at the 137th minute of CPB.

CPB was uneventful until the 204th minute when the FX05 started to show signs of decreased function (drop in the PaO_2 values despite the increased FiO_2). Initial trouble shooting involved increasing the sweep and FiO_2, however, PaO_2 continued to drop but the $PaCO_2$

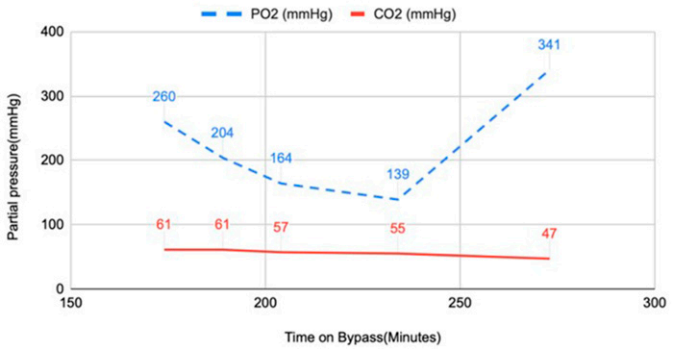

Figure 2. Graph showing the timeline and events for the pump oxygenator in case 1.

remained stable. The perfusionists used an external oxygen tank at 10 L/min of sweep in an attempt to increase oxygenation. After troubleshooting activities failed to improve oxygenation and at the 264th minute on bypass, the oxygenator was changed out.

The new oxygenator was primed in line once all connections to the circuit were made. The purge line on the oxygenator was used to deair before bypass was reinitiated (Figure 2 show the timeline). After the oxygenator change-out there were no further issues with oxygenation for the reminder of CPB. Throughout the bypass case the ACT remained above 655 for the entire case. Blood gasses were performed every 45 minutes. The CPB and the aortic cross clamp times in this case were 283 and 126 minutes, respectively.

Postoperative Course and Clinical Outcomes

The patient postoperative course and recovery were uneventful. Follow-up imaging showed normalization of right ventricular pressures and unobstructed flow in both branch PAs (Figure 1B) and she continued to do well during her follow-up with stable liver function tests.

CASE 2

Diagnosis and Preoperative Work-up

A 9.3 kg, 16-month-old child presented with a large secundum atrial septal defect (ASD) and Alagille syndrome with severe bilateral branch pulmonary arterial stenoses. The patient had confirmed JAG1 mutation. Preoperative CT scan showed (Figure 3A) severe bilateral branch pulmonary arterial hypoplasia with multiple stenoses, criss-cross branch PAs and patent ductus arteriosus. Other comorbidities included: history of pyloric stenosis, cutis marmorata telangiectatic congenita, complex coagulopathy with hypofibrinogenemia and hyperlipidemia. Table 1 shows preoperative laboratory work-up.

Cardiopulmonary Bypass Circuit Set-up

CPB equipments used included a 1/4-1/4 AV loop, FX05 oxygenator (Medtronic), CDI 500 (Terumo), bioconsole 560 arterial line flow probe (Medtronic), and HMS plus (Medtronic). CPB circuit was primed with 350 mL of RBC, 338 mL of fresh frozen plasma (FFP) washed with 600 mL of plasmalyte, 4.5 mg mannitol, 0.5 g magnesium, 10 mEq sodium bicarbonate, 125 mg of Solu Medrol, 3,000 units of heparin, 250 mL of 5% albumin, 250 mg Cefazolin, 37.1 mg TXA.

Conduct of the Procedure

The conduct of the procedure was similar to the first case. Dissection of all branch PAs was performed prior initiation of CPB and heparinization. Initial ACT was >999 seconds and heparin concentration was 4.8 mg/kg and CPB was initiated without difficulty via an aortic and right atrial cannulae. The core temperature was maintained at 34°C.

At approximately the 48th minute on CPB, the PaO_2 dropped to 120 mmHg from 210 mmHg. At this time the oxygen gas line filter was changed and switched to an oxygen tank at 10 L/min of sweep, despite these efforts the

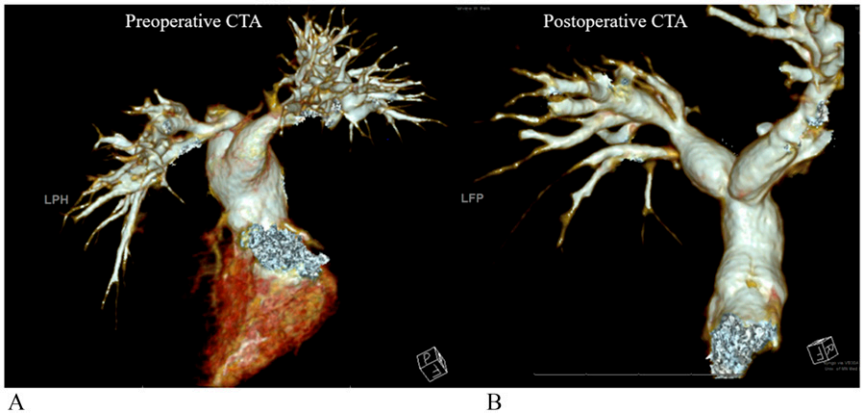

Figure 3. Branch pulmonary arteries as shown by 3D reconstruction of the computed tomographic (CT) scan (A) preoperatively and (B) after reconstruction.

PaO_2 continued to decrease. At the 78th minute on CPB, the arterial blood gas had a PaO_2 of 90 mmHg, so a decision to come off CPB and change out the oxygenator was made. At that time, the continuity of the right PA and the main PA was maintained, and the left PA was already disconnected, therefore, the lung was ventilated, and blood flow was maintained to the right lung, while the left PA site was clamped to support the patient while the oxygenator being changed. The FX05 was replaced with another FX05 and CPB was reinitiated without difficulty. First arterial blood gasses taken 14 minutes into second CPB, PaO_2 was 288 mmHg with an FiO_2 of 70% and a sweep of 1.2 L/min. Then at 34 minutes into second CPB, the PaO_2 dropped to 81 mmHg at an FiO_2 of 90% and a sweep of 1.5 L/min, the oxygenator was switched to an oxygen tank, but PaO_2 was continuing to drop. After 52 minutes, a second oxygenator change was performed and the FX05 was upsized to an FX15.

After the placement of the FX15, CPB was reinitiated for the third time without difficulty. Third CPB was uneventful until 53 minutes, where the PaO_2 slowly began to drop again and FiO_2 and sweep were adjusted to accommodate. Then at 128 minutes on the third CPB, the PaO_2 dropped to 72 mmHg on a 100%FiO_2 and 3.0 L/min of sweep. Third CPB was terminated at 147 minutes and the pulmonary arterial reconstruction was completed at that time. While off bypass, the circuit blood gas at 100% FiO_2 had a PaO_2 of 600 mmHg with the FX15 oxygenator. A fourth CPB was reinitiated to repair the ASD and the PaO_2 immediately dropped. At 7 minutes on bypass, the PaO_2 was 26 mmHg on 100%FiO_2 and 3.0 L/min of sweep. The ASD was closed swiftly, and the patient was weaned off CPB. During the duration of this case the lowest venous saturation was 63%, Refer to Figure 4 for timeline and data. Of note, the ACT was never reported below 665 seconds for the entire case and the heparin concentration was above 2 mg/kg.

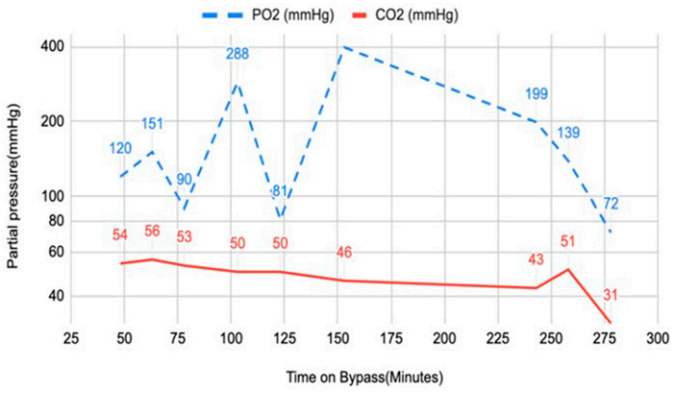

Figure 4. Graph showing the timeline and events for the pump oxygenator in case 2.

The total CPB and aortic cross clamp times were 301 and 9 minutes, respectively.

Postoperative Course and Clinical Outcomes

The chest was closed in a delayed fashion. The remaining postoperative course was uneventful and follow-up studies showed good biventricular functions, and widely patent branch PAs (Figure 3B). The patient's right ventricular pressure was 40% of the systemic blood pressure.

DISCUSSION

Oxygenator failure is a rare event but problematic event if it occurs during CPB. Several reports of potential causes of failure included elevated triglycerides levels, and microthrombosis associated with long CPB runs (8). We could not identify any reported CPB complications in the literature that are only unique to patients with Alagille's syndrome. Our experience prior to these two cases supports this as well and the usual expected complications are related to reperfusion lung injuries and those related to long CPB runs such as coagulopathy and/or hemolysis. The two current cases are unique, and the oxygenator failure in the first case was not connected to Alagille's syndrome, until the experience with the second one.

Potential Etiologies to Oxygenator Failures

Alagille syndrome as mentioned causes significant liver disease which affects triglyceride serum assay in patients which could be creating unwarranted oxygenator failure. As described by Badulak and associates, hyperlipidemia can decrease efficiency of the oxygenator membrane by producing a fatty layer that coats the membrane (7). This fatty layer decreases the surface area gas exchange and reduces oxygenator function. We have not checked the lipid profile in the first patient and we thought to rule out other possible etiologies. We have identified elevated triglycerides level in the second case which could have been attributed to the oxygenator failure.

Additional to hyperlipidemia, oxygen consumption is among the potential reasons for pump oxygenator failure. While we do not have a strong evidence to support this theory, the following two observations suggested the possibility of higher oxygen consumption: upon initiation of CBP, the venous blood was very dark and SvO_2 was in the 40s but it recovered after a few minutes of being on bypass, in addition to the circuit gas on the Rx15 which had a $PaO_2 > 600$. This value suggests that the oxygenator was working efficiently and suggests the patient could have had an increase oxygen consumption rate. This led us to conduct the CPB in the subsequent cases at much lower temperature.

Back-up Plan for Subsequent Case

When we were faced with a subsequent Alagille's case that required pulmonary arterioplasty, we prepared an additional oxygenator which was primped and clamped in a bridge as a back-up in case of failure of the main oxygenator. This option facilitates changing the oxygenator without interrupting CPB and minimizes risks associated with its sudden discontinuation, however, we did not use it due to implementing a different perfusion protocol.

Perfusion Protocol Changes in the Subsequent Cases

Perfusion protocol change was initiated after the second case to attempt decreasing the potential of future similar events. We have addressed the possibility of hyperlipidemia as the cause by upsizing the oxygenator from an FX05 to an FX15, AV loop from a 3/16-1/4 to a 1/4-3/8 and addressed the increase oxygen consumption by cooling the patient to 28°C in subsequent cases. The goal was to increase the surface area of the circuit to allow for dispersion of fatty molecules and creating a hemodilution affect, in addition to have an additional protective effect from hypothermia. Cooling to that temperature and rewarming does not significantly add additional time to the procedure in infants compared to adults.

Since we have implemented these changes in these unique cases, we have not experienced any oxygenator failure even with longer CPB runs.

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