Lymphatic Disorders in Patients with Single Ventricle Heart Disease

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Introduction

Percutaneous treatment of lymphatic diseases was reported by Cope et al. in 1995 [1], but it was not actively used because of the difficulty of cannulation into the lymphatic vessels. In 2011, Rajebi et al. reported intranodal lymphangiography for pediatric patients [2], which has been used to treat various lymphatic diseases of all generations. The causes of lymphatic diseases are diverse, including (i) traumatic lymphatic injury, (ii) lymphatic leakage related to increased venous pressure (mainly Fontan circulation), and (iii) lymphatic insufficiency (pulmonary lymphatic perfusion syndrome, chylous reflux syndrome).

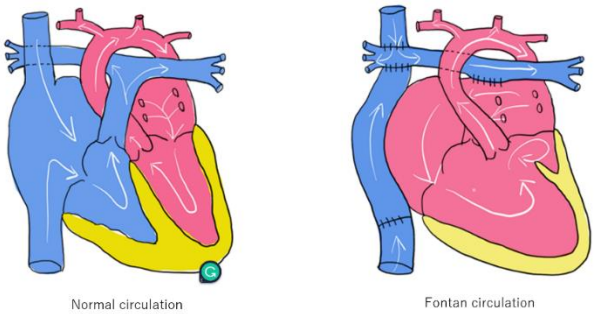
The symptoms are more complex in childhood. They include various conditions: neonatal chylothorax, postoperative chylothorax, chylous pericardium, plastic bronchitis, protein-losing enteropathy (PLE), chylous ascites, chyluria, lymph cutaneous fistula, and chylocorporrhea, etc. Diverse causes underlie these various symptoms. For that reason, we perform diagnostic imaging using lymphatic scintigraphy, ICG fluorescence lymphangiography, and dynamic-contrast MR lymphangiography (DCMRL), and select treatment according to the condition. Treatments include (i) therapeutic lymphangiography, (ii) lymphatic embolization, and (iii) lymph venous anastomosis (operated by a plastic surgeon), selected according to the pathological condition.

Congenital heart disease

Before the development of cardiovascular surgery, children with congenital heart disease reached adulthood at a rate of less than 50% of all live-born infants. By contrast, with the development of surgical treatment and improved medical management during the past half century, many pediatric patients with congenital heart disease are reaching adulthood. Today, more than 90% of children with congenital heart disease past infancy are adults.

The Fontan operation (Fig. 1)

Right heart bypass surgery is a crucial concept in treating complex cardiac malformations. In 1958 in the U.S., Glenn performed an anastomosis of the right pulmonary artery to the superior vena cava successfully for a 7-year-old single-ventricle case. Later, in France, in 1971, Fontan reported a functional radical procedure for tricuspid valve closure with anastomosis of the right atrium to the pulmonary artery. Since then, the operation has been improved incrementally. Its use continues to the present day.



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Lymphatic System in the Fontan Circulation

Lymphatic flow, which is unidirectional from the capillary bed to the subclavian vein, is maintained by lymph vessel contraction and by other factors. In the Fontan circulation, the pulmonary artery trunk is bypassed to the superior vena cava, thereby increasing the central venous pressure and the afterload of the thoracic duct. These phenomena cause the thoracic duct to dilate and become tortuous, forming multiple collateral blood vessels. The lymphatic system undergoes extravascular filtration throughout the capillary bed in accordance with Starling's law. The Fontan circulation leads to increased pressure in the lymphatic system. This increased pressure results in lymphatic stasis and various symptoms. The Fontan circulation has a target venous pressure of 10 mmHg. Any finding in excess of 15 mmHg is considered a Fontan failure.

What is Fontan Postoperative Syndrome?

The Fontan circulation intentionally maintains high venous pressure. The lymphatic system, which is connected directly to the subclavian vein, becomes congested and disrupted. Lymphatic leakage occurs in various sites after the Fontan procedure. In addition to fluid retention such as pleural, pericardial, and ascites effusions, lymphatic leakage into the airway results in plastic bronchitis (PB); leakage into the intestinal tract results in PLE.

Postoperative chylothorax

Chylothorax associated with Fontan surgery occurs in about 4% of cases. Its pathogenesis includes damage to the thoracic duct and lymphatic vessels, the physiologic elevation of venous pressure associated with right heart bypass surgery, and mechanical elevation of venous pressure because of obstruction of the superior vena cava or brachiocephalic vein [3].

In the Fontan circulation, pulmonary blood flow is susceptible to changes in intrathoracic pressure. The absence of negative inspiratory pressure during prolonged ventilation decreases pulmonary blood flow and cardiac output; it also contributes to venous blood and lymphatic stasis and might increase pleural fluid volume [4].

Diagnosis requires confirmation of the pleural fluid characteristics. If the differential count of blood cells in the pleural fluid includes more than 80% lymphocytes, then the diagnosis of lymphatic pleural effusion is possible. If triglycerides are greater than 110 mg/dl, then the diagnosis of chylothorax is possible. However, because triglycerides cannot be used to ascertain if the patient is fasting, if even a small amount of chylomicrons, which are excreted from the small intestine into the intestinal lymphatics, are present in the pleural fluid, then a diagnosis of chylothorax might be made.

Lymphatic scintigraphy is the most straightforward imaging technique. Moreover, it involves exposure but is very useful for pediatric patients. Magnetic resonance thoracic ductography (MRTD) is helpful in identifying the thoracic duct location and the venous angle.

A critical preoperative imaging study is the evaluation of the patency of the subclavian vein by echo or contrast-enhanced CT. Many post-Fontan patients have a PICC catheter inserted through the upper extremity, sometimes with thrombotic or inflammatory obstruction. Loss of venous angle outlet because of subclavian vein occlusion can cause chylothorax [5] and should be treated if recanalization is possible.

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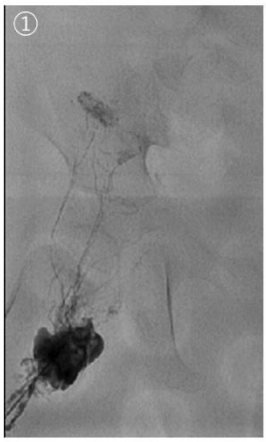
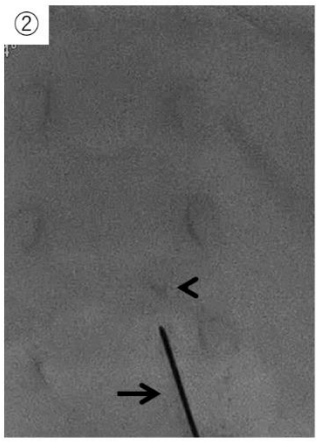
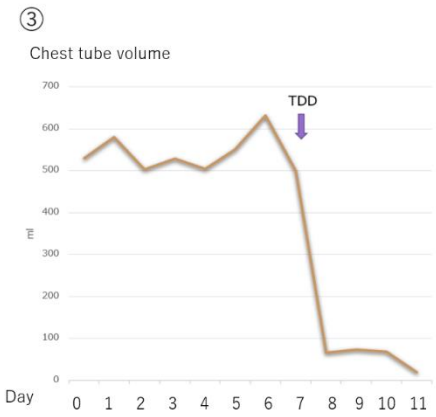
Case 1) Post-operative chylothorax







Fetal diagnosis: pulmonary atresia, ventricular septal defect, central pulmonary artery defect, major aortopulmonary collateral arteries.
At 11 months of age, right ventricular outflow tract reconstruction with central pulmonary artery formation was performed through a median sternotomy.
One month later, after an additional operation, the patient developed chylothorax (2000–3000 ml/day). Despite direct thoracic duct ligation and pleurodesis, the chylothorax did not improve (600–1000 ml/day). Lymphatic intervention was requested to save the patient's life.
(1) Lymphangiography with 1.5 ml of lipiodol from the right inguinal lymph node.
(2) Lymphangiography revealed a thoracic duct. TDD was performed: Arrow, 23G Chiba needle; Arrowhead, thoracic duct.
(3) Postoperative course: Pleural effusion improved immediately after TDD.

Plastic bronchiolitis (PB)
The formation of a thick plastic-like cast under the airway mucosa is characteristic of PB. Reportedly, it occurs in about 5% of patients with Fontan, resulting in chronic cough, hypoxemia, sputum, and sometimes asphyxia [6]. Although the pathogenesis of the disease is not yet fully understood, multiple highly dilated and tortuous thoracic duct and intrapulmonary lymphatic ducts are observed in patients with PB, secondary to elevated central venous pressure, resulting in stasis of the thoracic duct and lymphatic vessels. This stasis is thought to result from valve insufficiency of the intrapulmonary lymphatic vessels which normally carry flow from the lungs to the thoracic ducts. The valve insufficiency leads to backflow of cholesterol-rich lymph fluid traveling in the thoracic ducts into the intrapulmonary lymph vessels, eventually leading to leakage from the weakened areas in the airways.
The etiology of PB is lymphatic reflux into the left and right broncho mediastinal trunks, which run from near the venous angle to the anterior mediastinum, and into the pulmonary lymphatics, which run from the chest duct at the level of the tracheal bifurcation or diaphragm directly to the hilar region.
Its treatment involves intrapulmonary lymphatic embolization or thoracic duct embolization to prevent backflow from the thoracic duct to the intrapulmonary lymphatic vessels. The procedure is fundamentally identical to thoracic duct embolization.

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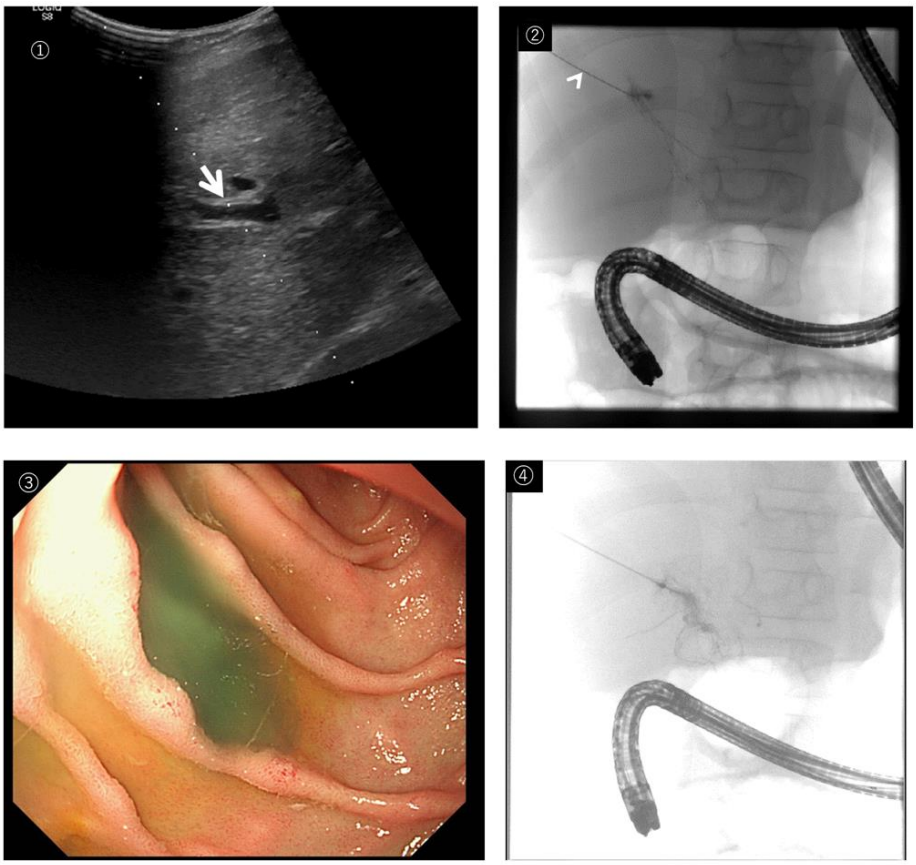
Protein-losing enteropathy (PLE)

Fontan-associated liver disease (FALD) results from chronic elevation of central venous pressure (CVP) and the consequent congestion of the inferior vena cava and hepatic veins, consequently increasing the portal venous pressure. The lymphatic fluid produced in the sinusoids is also increased, reportedly to 20 times normal [7].

Lymphatic fluid produced in the liver has a higher albumin concentration than that of peripheral blood or lymphatic fluid from other sites [7]. Three hepatic lymphatic pathways are (i) along the portal vein and through the duodenum to the cisterna chyli, (ii) along the hepatic veins to the thoracic duct at the level of the diaphragm, and (iii) along the liver surface to the thoracic duct. Of them, pathway (i) is essential for the pathogenesis of PLE.

Presumably, PLE is caused by a combination of increased liver-derived lymphatic fluid attributable to portal hypertension and increased pressure in the lymphatic system attributable to elevated central venous pressure, both of which lead to leakage of lymphatic fluid with high albumin concentration into the gastrointestinal tract. Treatment involves puncturing and embolizing the intrahepatic lymphatic vessels to prevent lymphatic fluid along the portal vein from passage through the gastrointestinal tract. By administering ICG through the puncture needle, the point of leakage can be confirmed by endoscopy if the leakage is from the duodenum.

Case 2)



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13-year-old boy after Fontan surgery. PLE
Hypoproteinemia appeared at the age of four years. Conservative treatment was performed, but the condition worsened gradually; daily albumin administration became necessary.
(1) The Disse space was punctured with a 23G Chiba needle (arrow).
(2) Iodine contrast medium was injected through the puncture needle (arrowheads).
(3) Indocyanine green was injected through the puncture needle. Leakage was observed from the duodenal wall using endoscopy.
(4) Intrahepatic lymphatic vessels were embolized with a 20% NBCA-lipiodol mixture injected through a puncture needle.
After embolization, abdominal pain appeared for 2 days, but it improved with management therapy. Preoperative abdominal pain and edema in the lower abdomen improved. However, the albumin level in the blood did not improve. The same procedure was performed one month later. The interval of albumin replacement was improved.

Treatment Outcomes
Lymphangiography : Lymphangiography. Lymphangiography can be performed in all cases. The lymph nodes in premature infants weighing less than 1 kg are extremely small. Therefore, lymphangiography is challenging to perform.

Chylothorax: If a leak is identifiable by lymphatic scintigraphy or other preoperative tests, then treatment is possible. It is often difficult for cases in which the point of leakage is not clearly identified. Especially in cases of subclavian vein obstruction, it is difficult to treat.

PLE: Long-term results have not been reported. In our experience, all severe cases relapsed within a year. In patients with mild disease, sustained elevation of blood albumin concentrations can be expected.

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