# Lymphatic Interventions in Congenital Heart Disease

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**KEYWORDS**

• Chylous effusions • Plastic bronchitis • Protein-losing enteropathy • Lymphatic disorders
• Thoracic duct • Lymphatic intervention • Dynamic contrast lymphangiography

**KEY POINTS**

- In the past decade, significant advances occurred in lymphatic imaging and treatment for lymphatic leakages and disorders in congenital heart disease patients.
- Traditional transcatheter interventions should be performed as first-line therapy to relieve any potential downstream thoracic duct obstruction and correct any anatomic concerns to decrease the overall central venous pressure and thereby lymph production.
- Selective lymphatic duct embolization (SLDE) has largely replaced total thoracic duct embolization as mainstay treatment. Recurrence of symptoms needing repeat interventions is more common in patients with SLDE.
- Novel surgical and transcatheter thoracic duct decompression strategies are promising, but long-term follow-up is critical and eagerly awaited.

## INTRODUCTION

The lymphatic system has largely been forgotten for the last few decades. With recent advancements in imaging modalities, the pathophysiologic aspects of the lymphatic system, especially in congenital heart disease (CHD), have been better understood.[1] This in turn has led to significant advancements in the treatment pathways for lymphatic disorders in CHD.

## ANATOMY AND PHYSIOLOGY

In addition to the well-known arterial and venous systems, the lymphatic system is the third and often forgotten circulatory system of the human body. The lymphatic system is present in most parts of the human body and plays a critical role in maintaining fluid homeostasis within the body. It regulates lymph drainage and aids in the transport of small molecules and solutes from various organs in the body. The lymphatic system serves 3 important functions, as follows:

1. Maintenance of fluid balance: The lymphatic system returns 15% of the fluid leaked out of the blood vessels into the tissues and interstitial spaces. The other 85% drains via venous capillaries and then via systemic veins to the right heart. The lymphatic system returns approximately the equivalent of the entire blood volume of the patient back to the heart every day.[2,3]
2. Immune function and regulation: The lymphatic system produces and releases lymphocytes and other immune cells, which provide immunity against various pathogens.
3. Absorption and transport of fat from the intestines: The lacteals, specialized lymphatic capillaries, in the intestines help absorb fats and fat-soluble nutrients from the villi of the small intestine and help transport them to the systemic veins.

One of the main functions of the lymphatic system is to collect and drain the lymph fluid back to the venous system of the heart. It

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consists of a network of lymphatic capillaries and vessels, lymph nodes, and the thoracic duct, which is the largest lymphatic vessel in the body.[2] The excess interstitial fluid in the organs is collected via initial lymphatic vessels/capillaries that drain into pre–collecting lymphatic channels, which subsequently coalesce to form the collecting lymphatic vessels. The lymphatic vessels resemble veins and have a one-way valve with few lymph nodes along their course. The collecting lymphatic vessels from the lower parts of the body and abdomen coalesce at the largest lymphatic collecting sac at T11-L1 vertebrae called the Cisterna chyli (Fig. 1). From the cisterna chyli arises the largest lymphatic duct in the body, called the thoracic duct, which collects lymph from bilateral lumbar trunks, intestinal/mesenteric duct, and the liver lymphatics. The liver contributes to about 40% of the total lymphatic fluid draining via the thoracic duct. Although there are multiple anatomic variants, most commonly a single thoracic duct courses cranially in the retroperitoneum, anterior to the vertebral bodies and midline/between the inferior vena cava and the aorta. After entering the chest compartment, it receives lymph from the heart and the lungs and traverses retrocardiac in the posterior mediastinum and eventually drains to terminate at the junction of the left innominate vein and left internal jugular vein. A one-way valve is typically present at the junction of the thoracic duct entrance to the systemic vein confluence. The thoracic duct drains three/fourths of the entire body and includes drainage of the entire lower half and the left upper part of the body. The right lymphatic duct is a short duct that drains the remainder of the right upper quadrant of the body (right arm, right chest, right side of the head and neck area) to the junction of the right subclavian vein and right jugular vein.

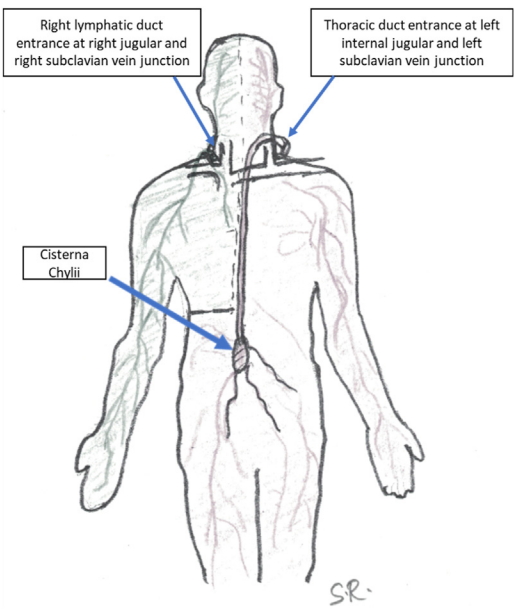


Fig. 1. Lymphatic drainage via the thoracic duct and right lymphatic duct. Lymphatic anatomy: thoracic duct and right lymphatic duct drainage regions.

### Special Considerations in Congenital Heart Disease

Patients with single- or two-ventricle CHD that leads to elevated central venous pressures are at highest risk of developing lymphatic leakages in the chest and abdominal compartment. Patients undergoing aortic arch intervention for coarctation of aorta or as part of Norwood arch repair and patent ductus arteriosus (PDA) surgical ligation are at risk for thoracic duct injury and/or disruption. Elevated central venous pressures, especially in single-ventricle-Fontan palliation patients, lead to chronic augmented hydrostatic pressure leading to significant increase in fluid filtration, and resultant interstitial fluid/lymph has to drain via the thoracic duct. This causes the thoracic duct to be congested and engorged with resultant dilation and tortuosity of the thoracic duct.[3,4] Fontan physiology leads to approximately a 5- to 20-fold increase in lymph fluid production causing "liver lymph flood" that eventually must drain to the left innominate vein, which is at the same hydrostatic pressure from which the lymph fluid was generated in the liver. This leads to engorgement and abnormal contractility of the thoracic duct and eventual reverse/centrifugal lymph flow resulting in patients' lymphatic symptoms.

## LYMPHATIC ABNORMALITIES IN CONGENITAL HEART DISEASE

### Lymphatic Abnormalities in Biventricular Patients

Patients with CHD often present with varying degrees of lymphatic abnormalities. In those with 2 ventricles, these abnormalities can manifest in distinct ways, impacting the course of the disease and treatment strategies. Lymphatic abnormalities in patients with two-ventricle CHD commonly involve impaired lymphatic drainage, which may result from increased central venous pressure owing to cardiac defects. Thus, any congenital heart condition either preoperatively or postoperatively that results in elevated central venous pressures, be it from ventricular diastolic dysfunction or obstruction in the venous

system (ie, innominate vein, superior vena cava, brachiocephalic vein narrowing or occlusions), can cause lymphatic disease. Elevated central venous pressure becomes the lymphatic afterload, which can result in poor egress of lymphatic fluid from the TD into the veins and the aforementioned upstream effects on liver production. It has recently been observed that those with specific congenital heart lesions, such as dextra transposition of the great arteries (d-TGA), heterotaxy and isomerism syndromes, pulmonary vein abnormalities, and arch anomalies, also have a baseline abnormal lymphatic anatomy that can provide the substrate for chylous leak.[1,5] This is especially true when the system is stressed or injured during cardiac surgery and in the postoperative period. These patients often exhibit symptoms such as peripheral edema, pleural effusions, and chylothorax. Understanding the precise nature of these abnormalities is crucial for tailoring interventions and improving outcomes.

### Lymphatic Abnormalities in Single-Ventricle Patients

In contrast, patients with one ventricle face unique challenges related to lymphatic abnormalities. The single-ventricle physiology alters the dynamics of lymphatic circulation, leading to a different set of clinical manifestations. Patients with single ventricle progress down a series of surgical palliations that work to balance the pulmonary to systemic blood flow and offload the ventricle. This, however, is at the expense of creating higher systemic venous pressure at each stage of the palliations. These patients manifest many lymphatic problems at the time of the Glenn surgery, wherein in the early postoperative phase, pleural effusions and pericardial effusions, can be common, up to 8%.[6] At the time of the Fontan, these central venous pressures are obligated to increase further ranging from 11 to more than 20 mm Hg. These patients then manifest another set of diseases related to lymphatic dysfunction, which include plastic bronchitis, protein-losing enteropathy (PLE), and ascites. What has been appreciated, however, is that patients can have terrible lymphatic dysfunction with relatively good Fontan hemodynamics (ie, low Fontan pressures, and low single-ventricular end-diastolic pressures). Conversely, not all patients with elevated Fontan pressures manifest lymphatic disease. The elevated central venous pressures related to Fontan circulation and the abnormal lymphatic substrate together lead to patients having clinically significant lymphatic dysfunction. Dori and Smith[1] and Dori and colleagues[5] have demonstrated that knowing the lymphatic anatomy of patients before undergoing Fontan completion can help to risk-stratify whether they will need intervention, and also which patients will fail as a Fontan owing to lymphatic disease.

## LYMPHATIC EVALUATION

### Lymphatic Evaluation

Lymphatic evaluation plays a pivotal role in diagnosing and managing various medical conditions. It allows clinicians to assess the lymphatic system's structure and function, aiding in the early detection of abnormalities and guiding treatment decisions. This section delves into the techniques and procedures used for lymphatic evaluation, which includes mapping the system, categorizing them into 2 main sections: noninvasive imaging and invasive imaging, and offers an approach to ensure a comprehensive evaluation of patients with lymphatic disease. When formulating a plan regarding a patient with a lymphatic disease, it is essential to be able to answer the following questions:

1. Is this a presentation of single compartment or multicompartment disease?
2. Is there an underlying genetic syndrome that has lymphatic implications?
3. Are there correctable hemodynamic causes for the lymphatic problem (ie, venous thrombosis, elevated filling pressures)?
4. What is the patient's structural and functional lymphatic anatomy?
5. Are the fluid dynamics that power the lymphatic system intact with low pressure and brisk flow into the venous system?

#### *Single-compartment disease*

The first question that needs to be answered is whether the lymphatic dysfunction involved a single compartment or multiple compartments. Single-compartment disease typically involves lymphatic leak within one specific area, such as isolated chylothorax, chylo-pericardium, ascites, or plastic bronchitis and so forth. Multicompartment disease refers to evidence of lymphatic dysfunction resulting in leak into multiple areas, for example, chylous ascites plus pleural effusions.

**Genetic evaluation.** Understanding if there is a known genetic entity or syndrome that contributes to lymphatic disease has become more important in the last 5 years of lymphology. Upward of 40% of patients with trisomy 21, for

example, will have some lymphatic dysfunction. Nearly all patients with genetic syndromes involved reticular activating system (RAS) mutations or RASopathies, such as Noonan syndrome, will have some lymphatic abnormalities. Other conditions, such as generalized lymphatic disease (GLA) and kaposiform lymphangiomatosis (KLA), Hennekons syndrome, and Gorham stout, further inform the clinician regarding how likely it is that the patients have a true lymphatic disorder, and for some, provide a roadmap for treatment. In patients with RASopathies, Noonan syndrome, for example, it is now well accepted that shutting down the thoracic duct with either surgical or percutaneous embolization results in devastating mortality and morbidity.[7,8] Moreover, in 2019, Dori and colleagues[9] discovered that MEK inhibitors, such as Trametinib therapies, could "prune" and resolve lymphatic dysfunction in most of these patients, many not needing any lymphatic interventions at all (Fig. 2).[8] As many of these tests and panels can take several days to weeks to return results, it is important to consider ordering these genetic tests early in the presentation of lymphatic.[8,10]

**Structural and functional anatomy.** The ability to image the lymphatic system has advanced significantly in the last 10 years. Older methods, such as lymphoscintigraphy, have given way to precise cross-sectional imaging in the form of high-fidelity MRI and functional ultrasound.[11,12] In order to comprehensively image the lymphatic system, it is important to understand the microarchitecture as well as how fluid travels through the system in a dynamic way. One essential element is performing a dynamic contrast-enhanced MR lymphangiogram (DCMRL). In this procedure outlined by Biko and colleagues[5], the practitioner places small stylet spinal needles with ultrasound and fluoroscopic guidance into 3 locations and secures them in place. A comprehensive evaluation involves needle placement in bilateral inguinal lymph nodes (IN-DCMRL), intrahepatic placement in the periportal lymphatics of the liver (IH-DCMRL), and intramesenteric placement (IM-DCMRL). Controlled gadolinium injection in these sites creates a clear picture with high special resolution of the entire abdominal, thoracic, and nuchal lymphatic systems (Fig. 3). By running dynamic sequences, one can follow contrast from the injection and in a time-resolved way over a period of 5 to 12 minutes, identifying the path of lymphatic fluid. Although the special resolution outlines anatomy and targets for interventions, this dynamic sequence reveals how the lymphatic anatomy has affected the flow dynamics of the lymphatic fluid as it courses through the body. High-volume leaks,

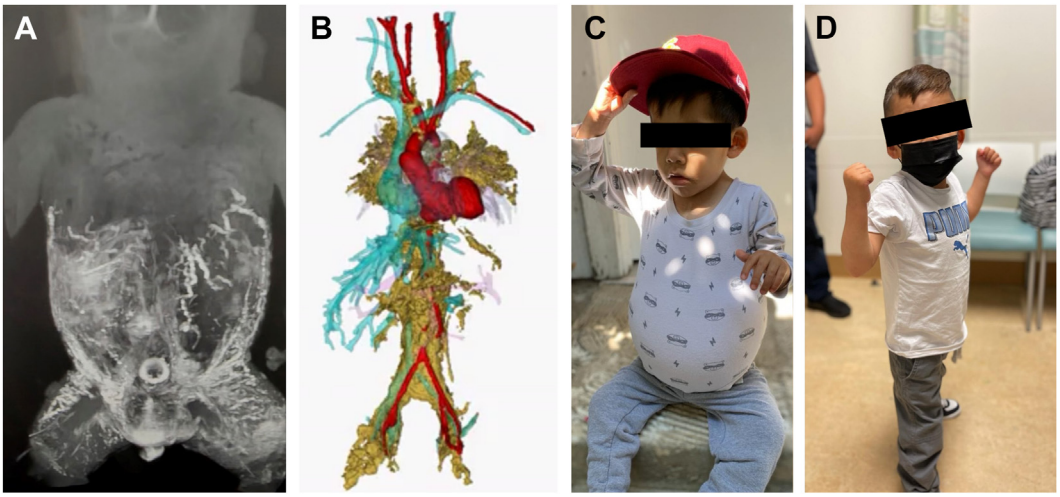


Fig. 2. Lymphatic disease in patients with RAS mutations. Patients with RASopathies, such as Noonan syndrome, have significant lymphatic dysplasias from an absence of severe central lymphatic flow disorder panels (*A*, *B*), to dilated "unpruned" lymphangiectasia (*C*). Arrows show dermal lymphatic back flow, which is a characteristic finding in patients with central flow disorder. The patient in panels C and D with Noonan syndrome had refractory chylothorax after cardiac surgery and severe lymphangiectasia seen on DCMRL. He underwent percutaneous thoracic duct embolization, which cured the chylothorax; however, immediately after, and for the subsequent 2 years, the patient suffered with severe chylous ascites. After the discovery of the effect of MEK inhibitors on RASopathies, this patient was started on Trametinib. He had complete resolution of his symptoms in 6 months and remains asymptomatic 1 year after completion of a year of treatment.

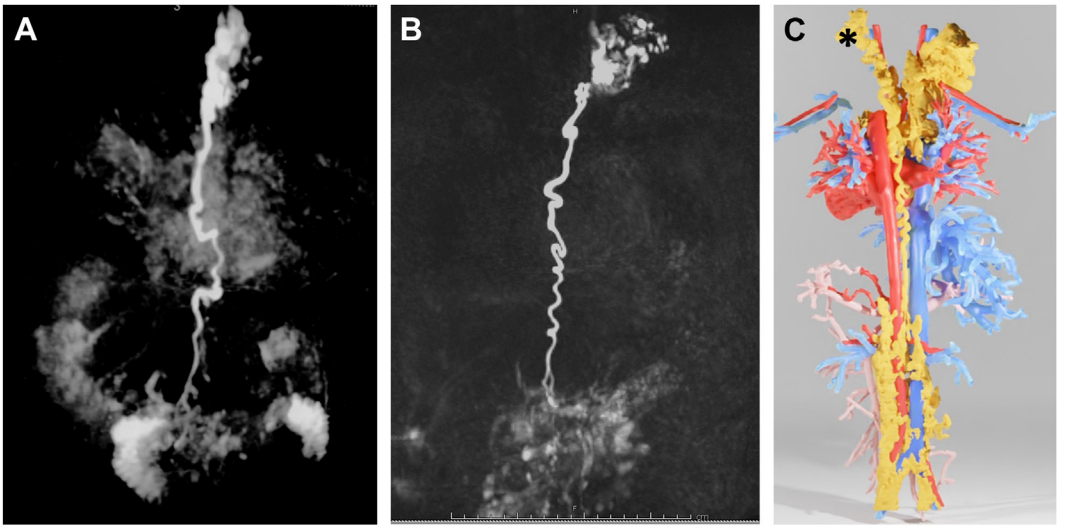


Fig. 3. Comprehensive dynamic contrast-enhanced MR lymphangiogram. Intrahepatic DCMRL (*A*), intramesenteric DCMRL (*B*), and 3-dimensional reconstruction of an intranodal DCMRL (*C*). Lymphatic anatomy from the IN-DCMRL (*asterisk*) overlying a feraheme cardiac MRI. Arrow points to the dilated and tortuous thoracic duct. Panel C shows the dilated and tortuous thoracic duct in yellow color.

for example, will fill early in the sequence, even before normal anatomy is seen.[12] Fig. 4 shows a patient with severe PLE and a high-volume leak caused by numerous abnormal hepatoduodenal lymphatic connections. In this case, the contrast is seen filling the lumen of the duodenum well before the thoracic duct fills. In more insidious leaks, as seen in plastic bronchitis or some chylous effusions, simple abnormal perfusion of these target areas can be seen clearly in this modality. Advancements in the technology have also shown the efficacy of heavy T2-weighted steady-state free precession imaging to view the larger structures of the lymphatic system in a noninvasive way. The benefits of this MRI sequence are that it does not require needle placement and can be added on easily to most other sequences. Although this modality does not provide the dynamic information that a DCMRL does, it can be an important screening adjuvant for lymphatic disease and can be performed even as a routine outpatient imaging study.[13,14]

**Ultrasound evaluation.** Although DCMRLs provide most of the information needed for

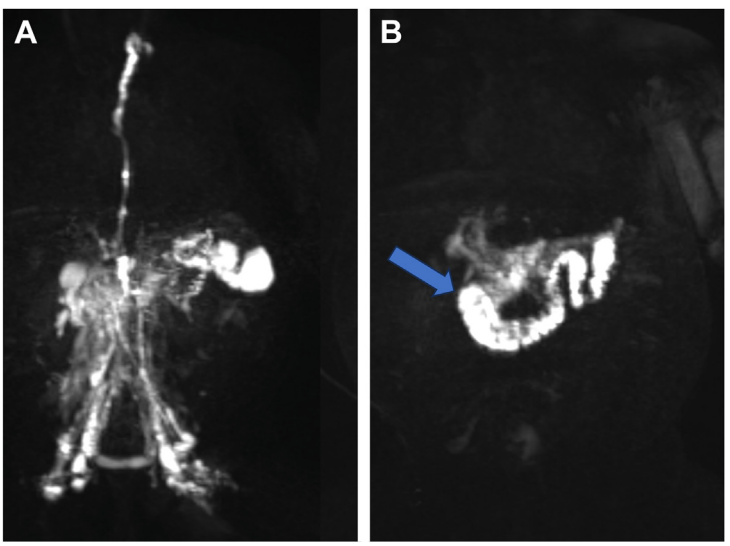


Fig. 4. DCMRL evaluation for PLE. Intranodal DCMRL in an infant with primary PLE demonstrating a mildly dilated but otherwise normal central thoracic duct (*A*). Intrahepatic DCMRL on this same patient shows immediate leakage and opacification of the duodenum (*arrow*) and distal small intestine without filling of the thoracic duct (*B*). This finding reflects the severe symptoms exhibited by the patient. These hepatoduodenal connections represent the radiographic signature for PLE.

preprocedural imaging, ultrasound plays an important role. This is to answer whether the thoracic duct is patent. Gao and colleagues[15] have shown that in adults, the thoracic duct outlet can be seen using superficial probes with near-field clarity. The anatomy of how the TD enters into the venous system varies from single entry with a bileaflet valve, to multiple fingerlike attachments to the left venous angle. Patency of the TD can then be determined by injecting a small quantity of echo contrast from the placed needles. With the ultrasound then switched to contrast imaging mode (low mechanical index), contrast flow can be seen from the lymphatic vessels entering the vein moments after injection from the inguinal nodes.

***Assessing thoracic duct flow dynamics.*** With the minimally invasive imaging complete, there is essential information that comes only from more invasive procedures. Once a comprehensive DCMRL and echo contrast evaluation have been completed, patients must be brought to the catheterization laboratory to assess hemodynamics. This involves, at minimum, a right heart catheterization to evaluate the venous filling pressures, with assessment of ventricular end-diastolic pressure by pulmonary capillary wedge assessment. Wedge angiograms of the thoracic inlet can also give information of the patency of the thoracic duct inlet.[16] Assuming a central TD exists, access to the thoracic duct must be conducted in either a retrograde fashion or a percutaneous, transabdominal manner. Direct access with a high-fidelity microcatheter (2.8F and up) will allow for pressure measurements. Normal values of the thoracic duct are still being defined depending on various anatomy; however, it should be 1 to 5 mm Hg higher than the central venous pressure to drive emptying. It is known, for example, that TD flow essentially shuts down with venous afterload pressures of 17 mm Hg or higher.[16,17] Higher TD pressures with low systemic venous pressures, for example, should raise concern for thoracic duct outlet stenosis or occlusion. Correcting this obstruction may result in resolution of the symptoms caused by upstream lymphatic congestions.[18] Taking the time to move through this comprehensive evaluation arms the practitioner with the information needed to guide the intervention. Without this information, it is exceedingly easy to cause more harm or perform unnecessary procedures that result in failure to treat the lymphatic problem.

A comprehensive lymphatic evaluation encompasses a range of noninvasive and invasive imaging methods. Each approach serves specific diagnostic and therapeutic purposes, allowing practitioners to tailor their assessments and interventions to the unique needs of patients with lymphatic disorders.

## LYMPHATIC INTERVENTIONS

Lymphatic abnormalities in patients with CHD can be broadly classified into innate or acquired. Innate or congenital lymphatic abnormalities are often noted in syndromic patients (Down, Turner syndrome, and so forth) who also have higher incidence of CHD. Patients with Down syndrome and CHD, such as atrioventricular septal defect, may be born with associated congenital central flow lymphatic abnormalities.[19] Such patients may have a history of hydrops fetalis or neonatal chylous effusions. Acquired lymphatic abnormalities in patients with CHD are noted after birth either owing to downstream outflow obstruction of the systemic veins (left innominate vein obstruction), traumatic injury to the thoracic duct during cardiac surgery, or excessive lymph production owing to significant alterations in central venous pressure (elevated central venous pressure [CVP]/Fontan pressures). In patients with central lymphatic flow disorder, commonly seen in syndromic patients with trisomy 21 and so forth, care must be taken to identify and treat distal thoracic duct outlet obstruction. Thoracic duct surgical ligation or transcatheter embolization is contraindicated in such patients.[18,19]

Treatment of lymphatic leakage should be geared toward both relieving the downstream anatomic obstruction to lymphatic drainage and correcting the anatomic or physiologic problem leading to lymphatic fluid overproduction or leakage. Patients with a Glenn palliation and noted to have a higher grade 4 lymphatic abnormality are at high risk for lymphatic disorders/Fontan failure, and their candidacy for Fontan palliation should be critically evaluated.[20,21] Any patient presenting with lymphatic leakage in the chest compartment (chylous effusions/plastic bronchitis) or in the abdominal compartment (PLE/chylous ascites) should be carefully evaluated to identify the main offender for lymphatic leakage.

### Nonlymphatic Interventions for Lymphatic Leakage

Traditional transcatheter interventions should be offered as first-line therapy to all patients with CHD presenting with lymphatic leakage. Traditional transcatheter interventions should be geared toward addressing anatomic and/or physiologic causes of lymphatic leakage, caused

by downstream obstruction or lymph overproduction. An example of an anatomic cause is innominate vein stenosis/obstruction leading to thoracic duct outlet obstruction. Examples of physiologic causes that lead to lymphatic overproduction include all right and left heart conditions leading to elevated central venous pressures. Elevated CVP, especially in patients with a single ventricle, can be caused by anatomic problems, including branch pulmonary artery stenosis, pulmonary vein stenosis, severe atrioventricular valve regurgitation, and systolic/diastolic ventricular dysfunction and recurrent coarctation. Elevated CVP related to the above conditions leads to a significant increase in the liver lymph production leading to what is termed the "liver lymphatic flood." This increased liver lymphatic flood must now drain via the thoracic duct to the same elevated CVP noted in the left innominate vein junction, thereby creating a perfect setup for reverse or centrifugal drainage of lymphatics in the thoracic compartment (more common) or in the abdominal compartment.[18,19]

In both patients with single ventricle and 2 ventricles, the left innominate vein obstruction leads to downstream thoracic duct obstruction. In the absence of any other thoracic duct decompression channels to the systemic veins, such patients more commonly present with either chylous effusions or plastic bronchitis. Identification of the downstream obstruction by ultrasound, computed tomography, or MRI modality followed by recanalization and balloon/stent angioplasty of the left innominate vein to reestablish patency of the vein helps relieve lymphatic leakage symptoms (Fig. 5). Other traditional transcatheter (balloon/stent angioplasty) procedures to relieve anatomic obstructions of the Glenn pathway or Fontan pathway or to relieve recurrent coarctation in patients with a single ventricle will help to relieve the overall pressures in the body. As soon as the CVP is reduced by a few points, many patients see a remarkable decrease in their lymph production with resultant resolution of lymph leakage symptoms. In patients with persistent or recurrent lymphatic leakage concerns following traditional transcatheter therapies, further lymphatic evaluation and treatment should be offered.

## Lymphatic Interventions

Lymphatic interventions have emerged as crucial tools in the management of various lymphatic disorders. This section explores the diverse range of interventions available, categorized into 3 main sections: central and lymphatic flow disorders, single-compartment leaks, and interventions for PLE.

### *Dietary modifications*

In mild cases of chylous leaks and PLE, dietary modifications play a critical role in reducing protein loss. Restricting dietary fat and administering medium-chain triglycerides can alleviate symptoms by minimizing chyle production and absorption.

### *Medications*

Medications such as corticosteroids, octreotide, and anti-inflammatory agents may be prescribed to manage inflammation and reduce protein loss in more severe cases of PLE. Data behind each have been lackluster, as many of the studies were conducted before the ability to image the lymphatic system. In regard to chylous leaks, the combination of maintaining a nothing-by-mouth status and starting Somatostatin analogues both work to decrease the blood flow to the gastrointestinal tract. This strategy relies on the hope that the branches off the thoracic duct that are causing the leak are small collateral vessels that will merely shut down if flow is not forced through them. This strategy of medical management works best with information from a DCMRL to confirm this anatomy. Recently, studies looking at the medication midodrine have shown promise in controlling some patients' symptoms with PLE. Midodrine and its class of medications work by drawing fluid out of the intravascular space, thereby alleviating third-spacing symptoms, but can also upregulate the contraction of the thoracic duct smooth muscle peristalsis. This can therefore help alleviate some symptoms, however only in the context of a patent thoracic duct.[22]

## Central and Lymphatic Flow Disorders

Central and lymphatic flow disorders often require interventions to restore normal lymphatic circulation and relieve symptoms associated with impaired drainage. Examples of this would be thoracic duct narrowing or stenosis, or, in some cases, complete obstruction. In these cases, intrathoracic duct stenting and angioplasty can be performed (see Fig. 5). In cases where there is obstruction in the distal thoracic duct by the venous angle, Lymphatic Bypass Surgery can be entertained. Lymphatic bypass surgery involves creating alternative pathways for lymphatic fluid to bypass obstructed or damaged lymphatic vessels. Procedures such as lymphaticovenous anastomosis (LVA) and lymphaticolymphatic anastomosis aim to

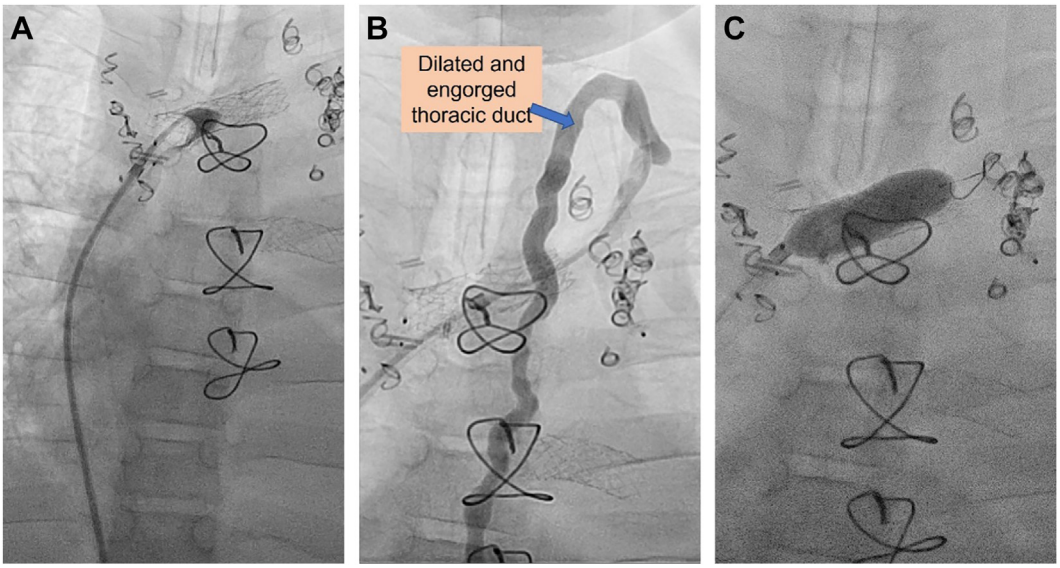


Fig. 5. Chylous effusions in a patient related to left innominate vein obstruction causing distal thoracic duct outlet obstruction. Downstream thoracic duct outlet obstruction in a 10-year-old patient with left innominate vein obstruction presenting with chylous effusions. (*A*) Complete occlusion of the stented left innominate vein. (*B*) An engorged and dilated thoracic duct (*arrow*). (*C*) Balloon angioplasty of the left innominate vein stent that led to a decrease in the size of the thoracic duct and resolution of the chylous effusions.

reestablish proper lymphatic flow (Fig. 6).[23,24] In these cases, thrombosis of the intervened on site can be common, and it is essential to anticoagulate as well as frequently confirm patency of the anastomosis/stented region with imaging. In some cases of central and lymphatic flow disorder, however, there can be a complete absence of intervenable lymphatic structures, and the creation of an LVA is not possible.

### *Lymphatic embolization*

Lymphatic embolization is a procedure in which embolic agents are injected directly into the leaking lymphatic vessel or node, effectively sealing the leak. This represents most interventions in patients with conditions like plastic bronchitis, lymphatic ascites, and chylous effusions by preventing the continued loss of lymphatic fluid. The most important goal of this procedure is to selectively access the branch or branches off of the main TD that is causing the leak. This is usually done after retrograde or percutaneous transabdominal access. Using a variety of techniques highlighted in Fig. 6; Fig. 7, vessels are accessed in a subselected way and embolized or excluded

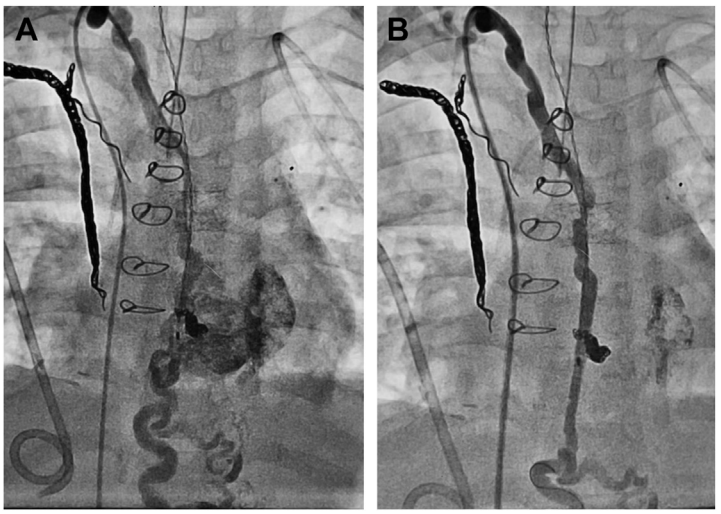


Fig. 6. Covered stenting of a complex TD leak after surgical LVA. A 3-year-old with a history of chylothorax after a Fontan procedure. DCMRL showed complete TD occlusion, so he underwent a surgical LVA (*arrow*). The LVA was then crossed anterograde, and the injection continued to show a complex leak from multiple sources (*blue bracket*). The patient therefore underwent covered stenting using a coronary-covered stent of the mid TD to exclude the leak. TD angiogram after stenting shows no contrast filling of area in the chest at all (*red bracket*).

using covered stents. Embolizing agents include micro-coils, liquid embolic agents such as Onyx (ethylene vinyl alcohol dissolved in dimethyl sulfoxide; Medtronic, Irvine, CA, USA), and N-BCA glue. Practitioners with experience in liquid embolic agents will create a dilution of the agents to ensure that the substance can travel in a controlled way into the target vessel alone. It is imperative to prevent inadvertent embolization of material into the venous system. If this happens, the agents can travel to the lungs and polymerize and compromise flow. If there is an obligate right-to-left shunt, as seen in patients with fenestrated Fontan, or pre-Fontan single-ventricle anatomy, embolic agents can enter the systemic circulation.[24] This can cause cerebral vascular events and end-organ injury. Work to repurpose safer embolic agents, such as sodium tetradecyl sulfate, is underway. This sclerosis agent has been used historically in the venous system, and its properties may prove safer from a side-effect profile than other glue-based embolic agents.

### *Thoracic duct embolization*

For patients with chylothorax or chylous ascites owing to thoracic duct leaks, thoracic duct embolization is a minimally invasive procedure. It involves blocking or sealing the leaking duct with embolic agents, effectively reducing lymphatic leakage and resolving the associated symptoms. In the modern era of lymphatic intervention, this should be considered only as a last resort, and, as mentioned before, is contraindicated in patients with central lymphatic flow disorder (CLFD), multicompartment disease, and a relative contraindication in patients with single-ventricle palliation. The lymphatic system is being rediscovered as a true circulatory system, regulated by pressure differentials and responses to preload and afterload, and possesses action potentials and the capacity for pacing. This in combination with the proclivity to lymphangiogenesis has revealed that large alterations, such as complete shutdown of the thoracic duct, can have severe downstream affects as seen in previous examples.

## Interventions for Protein-Losing Enteropathy

PLE in patients with Fontan circulation is a complex condition that requires specialized interventions to manage protein loss and associated symptoms. Imaging breakthroughs by Smith and Dori[1] have shown that PLE results in direct connection of abnormal lymphatic vessels eroding into the mucosa of the duodenum. These are abnormal hepatoduodenal and mesenteric-duodenal connections. This results from overproduction of lymphatic fluid from the liver secondary to elevated, and nonpulsatile ventral venous pressure. This congests the lymphatic egress from the liver and upstream in the mesenteric lymphatic drainage, which results in engorgement of the periduodenal lymphatic vessels and eventual erosion into the luminal mucosa. This can be

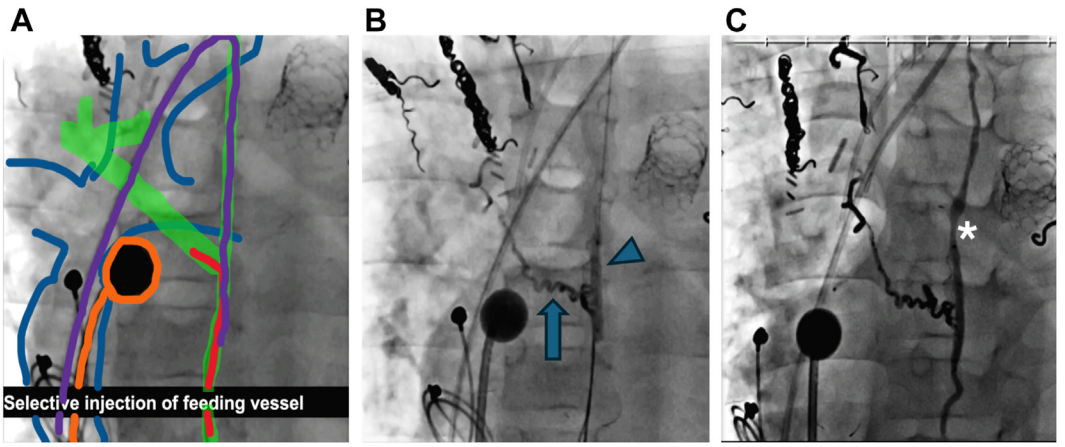


Fig. 7. Selective embolization of a lymphatic vessel causing severe plastic bronchitis. A 17 year-old with a Fontan and severe plastic bronchitis (PB). Technique for selective embolization of the feeder vessel. A 2.4F microcatheter is placed anterograde into the leaking vessel and TD (*green line*) from a percutaneous anterograde fashion (*red line*). A 4-mm coronary balloon advanced form the right femoral vein in a retrograde approach used to temporarily occlude the mouth of the TD to ensure no glue refluxed into the TD (*purple line A* and *arrowhead B*) Fontan (*blue line*) seen with a wedge catheter balloon occluding the Fontan fenestration to prevent paradoxic emboli (*orange line*). (A) With this system in place, the lymphatic vessel causing the PB is selectively embolized (*arrow*). (*B*) Selective angiogram of the TD showing patency after glue embolization of the feeder vessel after coronary balloon was removed (*bracket*) (*C*).

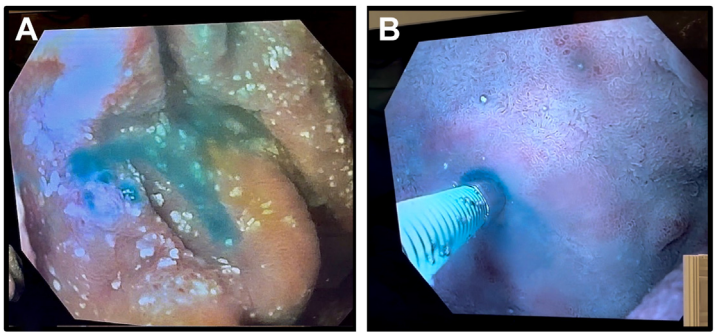


**Fig. 8.** Endoscopic treatment of PLE. Endoscopy during lymphatic intervention for PLE shows dilated lacteals in the duodenum with brisk flow of isosulfan blue dye injected from the hepatic lymphatics (*A*). Isosulfan blue dye is seen emerging from the duodenum during endoscopy (*B*) Direct endoscopic embolization of a "lymphatic spout" using a 25-gauge endoscopic needle.

seen in the IH- and IM-DCMRLs and elegantly seen during the intervention.[24]

During the intervention, access is achieved to the hepatic lymphatics with a 25-gauge spinal needle. Isosulfan blue dye is then injected from this site with simultaneous endoscopy. In real-time, moments after injection, streams of blue dye can be seen pouring into the lumen of the duodenum (Fig. 8). Goals of interventional treatment are then to occlude these "spouts." The 2 main approaches to this have been to occlude these from a percutaneous approach versus an endoscopic approach. In the percutaneous approach, a 25-gauge needle is used to selectively engage the periduodenal network of lymphatics and inject a thin-liquid embolic agent to "seal" the leaks. A marker of procedural success is repeat injection of blue dye from the hepatic access and the absence or decrease in dye seen entering the duodenum. The combination of embolic injection from the hepatic access and the periduodenal approach has shown remarkable short- and mid-term efficacy with stabilization of albumin levels, and improvement in symptoms. Rabinowitz and colleagues[20] have published results from an endoscopic approach wherein the "leaking spouts" are targets by the endoscopist, and a long 25-gauge needle is inserted from the endoscopic catheter and injected directly into these leaking areas. Data published from this group, although still with only 2-year follow-up, have similar promising results.[24]

### *Surgical and hybrid interventions*

For refractory PLE cases, surgical interventions like the Fontan completion revision or cardiac transplantation may be considered. These procedures address the underlying cardiac issues contributing to PLE and can significantly improve outcomes. In many cases, the clinical sequalae of long-standing, severe PLE can render the patient so ill, nutritionally depleted, and clinically unstable for Fontan revision or transplantation. In an effort to improve their candidacy and for these procedures, patients undergo a thoracic duct decompression procedure. This procedure involves placing a large sheath into the thoracic duct, often from a subclavian vein approach. With this in place, the thoracic duct is drained to decompress the system. After a period of decompression, contents are then autotransfused via venous access. This works to significantly reduce the interstitial fluid burden. Patients are then stratified to see whether they would benefit from a thoracic turn-down procedure wherein the innominate vein flow is diverted to the left atrium in a surgical or transcatheter procedure.[24] This procedure works only if the ventricular end diastolic pressure or left atrium pressure is sufficiency low enough to receive the lymphatic fluid. If this is not an option, or often in concert with this procedure, patients can sometimes become better transplant candidates. Advancements in this surgical arena are developing with lymph venous anastomosis to pulmonary veins and even intrathoracic azygous connections. Safety, efficacy, and longevity of these novel procedures have yet to be seen.

In summary, lymphatic interventions encompass a broad spectrum of procedures and strategies tailored to address various lymphatic disorders. Understanding the specific needs of patients with central and lymphatic flow disorders, single-compartment leaks, and PLE is essential for selecting the most appropriate intervention and optimizing patient outcomes.

## SUMMARY

Over the past decade, significant advancements made in lymphatic imaging have led to a better understanding of the pathophysiology of lymphatic abnormalities in patients with CHD. This has allowed the lymphatic system to regain its importance over the last decade, as novel

transcatheter lymphatic therapies have been performed and newer management algorithms have been developed to treat patients with CHD with various lymphatic abnormalities. Noninvasive T2-weighted lymphatic imaging is a critical screening test and should be routinely performed in all patients with a single-ventricle form of CHD undergoing a cardiac MRI. Invasive DCMRL imaging is currently limited to those patients suffering from symptoms of lymphatic leakage and who are being evaluated for lymphatic interventions. Caution should be exercised in patients with a single ventricle presenting with lymphatic complications early in life, and care must be taken to critically evaluate their candidacy before progressing their care to next-stage single-ventricle palliation. Selective embolization of the culprit lymphatic vessel or vessels identified to be causing the patient's symptoms is the mainstay of lymphatic intervention. For the past couple of decades, surgical thoracic duct ligation, and more recently, transcatheter thoracic duct embolization of the entire thoracic duct used to be the main form of lymphatic intervention. With improved knowledge of the pathophysiology of lymphatic disease especially in single-ventricle patients, effort is made to maintain patency of the thoracic duct so that patients will continue to have other novel lymphatic therapeutic options available for them in the future. Total thoracic duct embolization is now limited to only a handful of patients in whom selective lymphatic embolization has failed or if a patient's critical symptoms necessitate complete occlusion of the thoracic duct. A novel surgical or transcatheter left innominate vein turn-down procedure as part of the lymphatic decompression strategy for high-risk single-ventricle patients has shown initial promise, and long-term results are eagerly awaited.

## CLINICS CARE POINTS

- Over the past 2 decades, significant advances have been made in the diagnostic and interventional care of lymphatic disorders.
- Lymphatic disorders in children occur either due to a genetic abnormality or worsened by congenital heart disease and several other organ disorders.
- Dynamic contrast magnetic resonance imaging (DCMRL) has become the mainstay for diagnostic evaluation of lymphatic disorders.
- Selective lymphatic duct embolization is preferred over total thoracic duct occlusion especially in patients with single ventricle physiology.
- Thoracic duct occlusion is contraindicated in central flow lymphatic disorder patients.
- High grade (4) lymphatic abnormalities noted during pre-Fontan evaluation is considered one of the high-risk factors for Fontan failure and should be a relative contraindication.

## DISCLOSURE

None related to this article for both authors.

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