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ORIGINAL STUDIES

Percutaneous embolization of lymphatic fistulae as treatment for protein-losing enteropathy and plastic bronchitis in patients with failing Fontan circulation

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Abstract

Background: To determine the feasibility and clinical result of selective embolization of hepatoduodenal or paratracheal lymphatics in Fontan patients with protein-losing enteropathy (PLE) or plastic bronchitis (PB).

Methods: Dilated lymph vessels in periportal (PLE) or paratracheal (PB) position were percutaneously punctured with a 22G Chiba needle. Intralymphatic position was confirmed by water soluble contrast injection with drainage to hepatoduodenal or tracheal fistulae. After flushing with 10% glucose solution, occlusion of hepatoduodenal or paratreacheal lymphatics was effected by injection of 1–4 cc mixture 4/1 of Lipiodol/*n*-butyl cyanoacrylate (n-BCA; Histoacryl).

Results: Seven patients with proven PLE were treated with periportal lymphatic embolization 10.7 (range: 6.6–13.5) years after the Fontan operation. The Fontan operation was performed at a median age of 3.7 (range: 2.9–5.7) years and PLE started a median of 3.1 (range: 0.9–4.7) years later. Five patients required a second procedure 2–8 months later. Complications were limited (spillage of glue in portal branch, transient cholangitis, and caustic duodenal bleeding). Six of seven patients reported significant improvement in quality of life and normalization of albumin levels after limited follow-up ($p < .01$). One patient (Fontan at 2.9 years; age 16.4 years) had PB for 2 years. Selective transthoracic cone-beam-directed puncture of left and right paratracheal lymphatics with n-BCA embolization of distal lymphatic fistulae resulted in lasting absence of tracheal casts (11 months).

Conclusions: Embolization of periportal/peritracheal lymphatics is a promising technique in Fontan patients with PLE/PB. Larger series are required to determine incidence and reasons of success/failure, with long-term results and effects on liver function.

KEYWORDS

congenital heart disease, lymphangiography, lymphatic embolization, n-butyl cyanoacrylate, plastic bronchitis, protein losing enteropathy

1 | INTRODUCTION

Protein-losing enteropathy (PLE) following the Fontan operation is a vexing problem which occurs in 3–20% of patients.[1–3] Although mortality has improved from the initial almost 50% at 5 years to survival of 88 and 72% after 5 and 10 years, respectively, PLE remains a major cause of mortality and morbidity in this group of patients.[1,4] There are many similarities to plastic bronchitis (PB) which occurs in 4–14% of Fontan patients and may present by itself or in combination with PLE.[5,6]

Several medical and surgical strategies have been employed to treat PLE and PB, all with variable but modest degrees of success.[1,4,7,8] The role of the lymphatic system has been largely ignored in the management of the failing Fontan. Hraška demonstrated that surgical decompression of the ductus thoracicus by diverting it to the lower pressures of the systemic atrium, albeit at the expense of mild desaturation, provided relief for patients with PLE.[9] The excellent work of Itkin and coworkers refocused attention on selective percutaneous lymphatic embolization in the treatment of PLE and PB.[10–14] They elegantly proved hepatic lymph leakage into the duodenum via hepatoduodenal communications by injecting a dye into the periportal lymphatics and observing drainage into the duodenum using endoscopy[12]; they similarly demonstrated the lymphatic leakage into the trachea in patients with PB.[14] Percutaneous obliteration of these lymphatic fistulae resulted in reduction of lymphe leakage to subclinical levels, supporting this technique as an additional treatment option of PLE and PB.[10–14]

The pathophysiology of both PLE and PB is still poorly understood but undoubtedly relates to the unnatural hemodynamic conditions created when establishing a Fontan circuit. The chronic elevation of the central venous pressure after the Fontan operation has unfavorable effects on the hepatic and portal circulation resulting in increased interstitial fluid and lymphatic pressures.[15] Furthermore, impaired drainage of thoracic duct lymph with potential failure of valves at the lympho-venous connections occur.[15–17] The net effect of the altered hemodynamics is impaired lymphatic drainage and increased lymphatic pressures, overdistention, and rupture of lacteals with leakage and even retrograde lymphatic flow into low-pressure lumens, for example, the gut and bronchi.[15,18] This has been demonstrated by Ludwig in a post-mortem study where overdistention and rupture of the hepatoduodenal lymphatic connections were observed in patients with congestive heart failure and cirrhosis.[19] However, even though all Fontan patients are victims of an elevated CVP, not all develop PLE. This suggests local lymphatic problems, with possible additional causes such as diminished cardiac output, increased mesenteric vascular resistance, inflammation/infection, intestinal cell heparan sulfate depletion, or other factors.[10,20–22]

The aim of this article is to report our initial experience of using selective lymphatic embolization for the treatment of PLE or PB in patients following a Fontan operation.

2 | METHODS

This is a retrospective evaluation of selective hepatoduodenal or paratracheal lymphatic embolization as a treatment modality for children presenting with PLE or PB after Fontan operation. Demographic, clinical, and imaging data were obtained from hospital records. Written informed consent was obtained as well as approval by the UZ Leuven Medical Ethics Committee.

Selective percutaneous lymphatic embolization of hepatic or paratracheal lymph vessels was performed based on reported methods.[10,23,24] All procedures were performed under general anesthesia. Using ultrasound guidance, a 22-gauge Chiba needle was inserted percutaneously into the liver parenchyma, close to the hilus next to the portal vein. A water-soluble iodinated noncaustic contrast agent (Ultravist, Bayer HealthCare, Whippany, NJ) was injected to identify the dilated lymph and lacteal vessels. The desired needle position for embolization treatment was reached when the hepatoduodenal lymphatic vessels were demonstrated with run-off toward or even into the gut. These lymphatic vessels in Fontan patients are typically dilated.

For the embolization procedure, a 1:4 mixture of 0.5 ml *n*-butyl-2-cyanoacrylate (NBCA; Histoacryl, B. Braun, Barcelona, Spain) with 2.0 ml Lipiodol (Guerbet, France) was used. In order to prevent premature polymerization of NBCA after contact with ions, the needle and the lymphatic vessels were first flushed with a 10% glucose infusion. Subsequently, the glue was injected under fluoroscopic guidance, aiming to fill the distal saccular vessels before coagulation occurred, until no more progress was observed distally and proximally (Figure 1). Typically, 1–4 cc was required. The needle was then removed and local pressure applied to the puncture site; in two patients with ascites, the needle track was obliterated with the glue upon withdrawal. Abdominal ultrasound was performed early and after 2 hr to confirm absence of leakage into the peritoneum; the patients were monitored overnight.

The patient with PB was first investigated with inguinal lymphangiography. Cone-beam computer tomography (CT) showed dilated lymphatic vessels with the Lipiodol. We therefore decided to target analogous to the periportal technique these dilated paratracheal lymph vessels in the paratracheal chain.[16] Direct transthoracic puncture of the left and right para tracheal lymph vessels under fluoroscopic, cone-beam CT (Philips Healthcare, Best, Nl with XperGuide software) and ultrasound guidance was performed in order to avoid puncture of the intrathoracic structures using standard techniques.[25,26]

3 | RESULTS

Patient's cardiac diagnosis and demographic data can be viewed in Table 1. Seven patients presented with confirmed PLE and one with a PB (patient 8) after Fontan. Pacemakers were implanted in three patients because of underlying basal junctional bradycardia and stent enlargement of Fontan conduit in two.

The Fontan operation was performed at a median age of 3.7 (range: 2.9–5.7) years and PLE started a median of 3.1 (range: 0.9–4.7) years after the Fontan operation. The patients were treated at a median age of 14.9 (range: 10.3–16.5) years and at a median period of 10.3 (range: 6.6–13.1) years after the Fontan operation. PB started 10 years after the Fontan operation in patient 8.

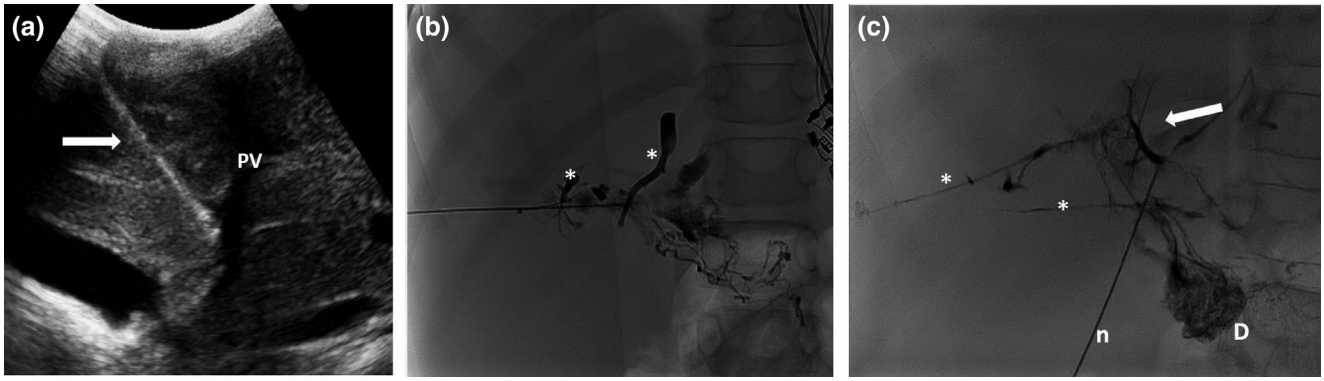

FIGURE 1 Periportal NBCA embolization of dilated hepatoduodenal lymphatic vessels for PLE. (a) Transhepatic puncture under ultrasound guidance (patient 1). Needle (arrow) can be seen in close approximation to PV. (b) Right-sided Lipiodol–NBCA lymphatic lacteals filled and occluded in patient 2. (c) Small hepatic veins embolized (*). Patient 5: glue being injected into dilated hepatoduodenal lymph vessels. The glue entered a small branch of the portal vein (white arrow). Tract of right-sided periportal punctures visible with glue in transhepatic tract (*) to seal off tract and prevent hemorrhage into ascites. Filling and occlusion of lacteals with duodenal spillage (D) can be observed. Needle (n) still in periportal lymphatics. NBCA, *n*-butyl-2-cyanoacrylate; PV, portal vein

TABLE 1 Patient characteristics

No	Symptom	Diagnosis	Age (year) procedure	Time (year) after Fontan	Medication	CVP (mm hg)	Alb (g/L) pre	Alb (g/L) f-up	Time after initial occlusion (month)	Number of procedures	Outcome
1	PLE	DORV, borderline LV	16.5	13.1	Diu, Bud, Bos	23	21	40	17	1	Stopped Diu, Bud, Bos
2	PLE	MA, TGV, VSD	10.3	6.6	Bud, Sild, ACE	15	20	34	11	2	Stopped Diu, Bud, ACE
3	PLE	HLHS	14.1	10.3	Diu, Bud, ACE	14	28	41	12	2	Stopped Diu, Bud, ACE
4	PLE	HLHS	14.9	11.0	Diu, Bud, Sild	17	22	37	10	2	Stopped Diu, Bud, Bos
5	PLE	DIRV, DORV	13.3	7.7	Diu, Bud, Sild	12	27	40	7	1	Stopped Bud
6	PLE	HLHS	15.4	9.6	Diu, Bud, Sild	18	18	49	5	2	Stopped Diu, Bud
7	PLE	HLHS	15.6	11.6	Diu, Bud, Sild	20	20	22	4	2	No change
8	PB	DILV, TGV	16.4	13.5	Inhal, bronch	20	37	N/A	11	1	Stopped inhal, bronch

Abbreviations: ACE, angiotensin converting enzyme inhibitor; Bos, bosentan; bronch, bronchoscopic extraction of bronchial casts; Bud, budesonide; DILV, double inlet left ventricle; Diu, diuretics (Furosemide, Spironolactone); DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; inhal, inhalation aerosols; LV, left ventricle; MA, mitral valve atresia; NA, not applicable; PB, plastic bronchitis; PLE, protein-losing enteropathy; Sild, sildenafil; TGV, transposition of the great vessels.

In all PLE patients, dilated hepatoduodenal lymphatic ducts were demonstrated. NBCA was successfully administered in the selected distal lymphatics via the 22G Chiba needle and occlusion was obtained in all patients (13 procedures in eight patients). A second procedure was required in five patients (three early at 2 months because of insufficient effect, two late after 8 months because of recurrence after initial normalization), whereby the lymphatic vessels on the same and opposite side of the portal vein were punctured and embolized. In patient 5 who presented with ascites, the peritoneal fluid was first drained to allow easier and more stable access to the liver; the periportal lymph vessels were punctured at three locations around the portal vein with subsequent embolization of all lymphatics. Upon withdrawal of the needle, the puncture passage was also obliterated with the NBCA mixture to avoid leakage into the peritoneal cavity (Figure 1).

The patient with PB was coughing up casts and had several previous bronchoscopies. The abnormal mediastinal lymphatic drainage was confirmed by inguinal intranodal lymphoangiography using Lipiodol. This showed that the thoracic duct had accidentally been ligated by a surgically placed clip used during arch repair in infancy; the contrast progressed diffusely into the mediastinum and neck region (Figure 2b). Cone-beam CT demonstrated dilated thoracic paratracheal lymph ducts (Figure 2). Percutaneous embolization was carried out by direct puncture of the left and right paratracheal lymph node chains and injection of NBCA under cone-beam CT guidance (Figure 2).

After the first procedure, four of seven patients showed an immediate response with normalization of albumin; an early second procedure was performed in the three nonresponders with good result in two. In two patients, after initial normalization of albumin, PLE reoccurred after 7–8 months; a second procedure was again able to reduce the enteric

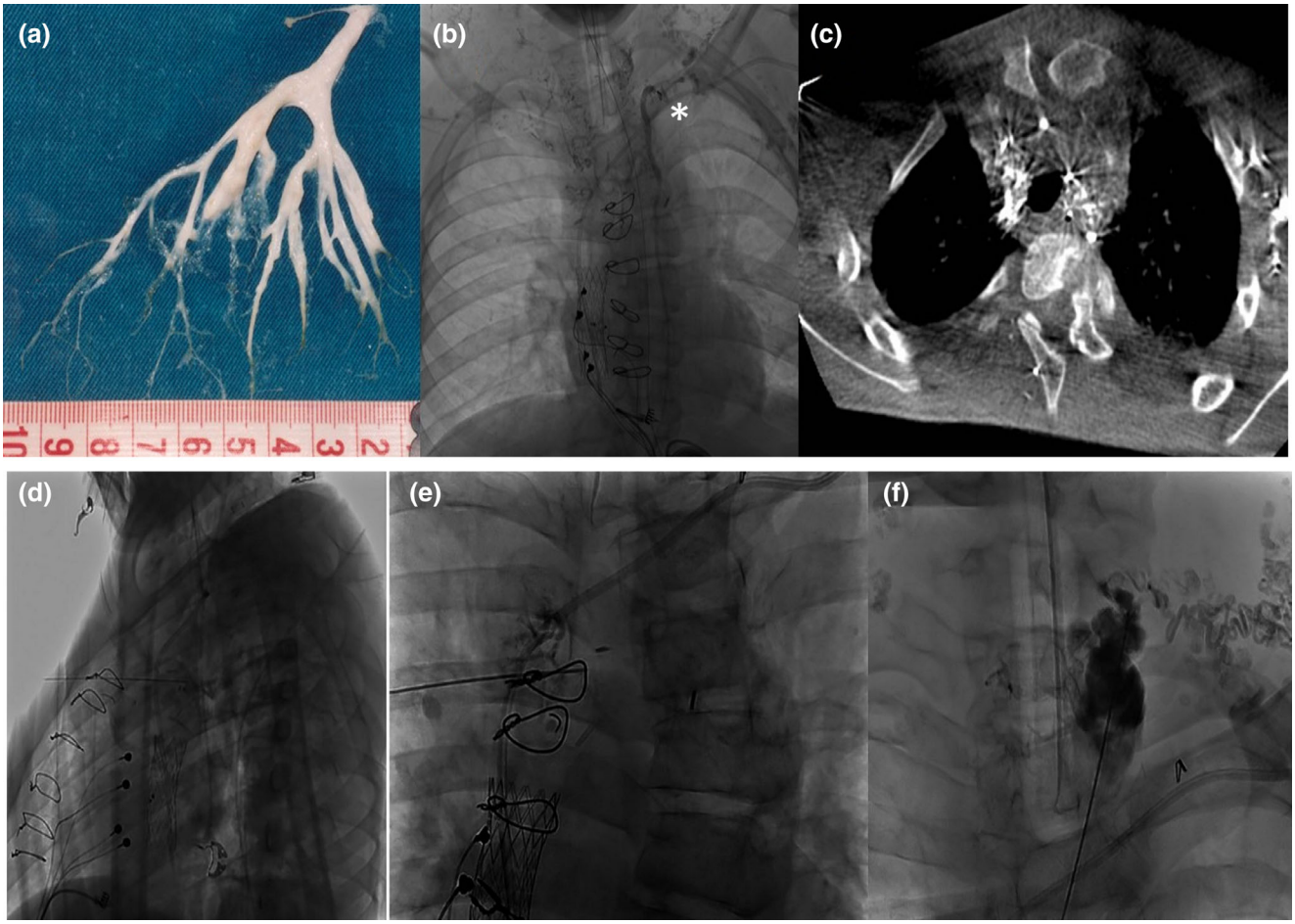

FIGURE 2 Plastic bronchitis. (a) Expectorated cast of bronchial tree in Fontan patient with PB plastic bronchitis. (b) Lymphography after inguinal intranodal Lipiodol injection: thoracic duct is opacified and a surgical clip is observed at the junction with subclavian vein (accidentally placed during neonatal coarctectomy*)—note progression of Lipiodol contrast in upper mediastinal lymphatics. (c) Cone-beam computer tomography of mediastinum after inguinal Lipiodol infusion: thoracic duct, with contrast in multiple dilated lymph vessels. (d) Lateral view percutaneous direct transthoracic cone-beam computer tomography guided puncture of paratracheal lymph vessels with 22G Chiba needle. (e) Frontal view of puncturing at right side of trachea. (f) Paratracheal puncture on left side [Color figure can be viewed at wileyonlinelibrary.com]

protein losses to subclinical levels. In the six of seven responders, albumin improved significantly from a mean of 23.0 ± 5.1 g/L to a mean of 40.7 ± 5.2 g/L ($p < .01$); patient 7 never responded despite an aggressive second procedure (which was complicated by caustic duodenal bleeding). In all of six responders with PLE, diuretics, steroids were stopped within a month; pulmonary vasodilators were maintained in three patients with increased pulmonary vascular resistance. Two patients had ascites and mild improvement was observed in one patient. All successful patients (six of seven) reported improvement in quality of life, especially reduction of diarrhea and abdominal bloating.

Bronchial casts remained absent in the patient with PB after 11 months of follow-up.

No major intraprocedural or periprocedural complications were observed and patients were discharged after 48 hr. In one patient, some of the NBCA was spilled and caused glue protrusion into two small portal veins and in a hepatic vein without any ill effects (Figure 1).

Two patients had a "late" transient complication 4 and 7 days after a second procedure, where we aimed for maximal obliteration: patient 6 was readmitted for transient cholangitis (pain and congested bile but no infection); patient 7 presented with melena due to caustic bleeding from the duodenum.

4 | DISCUSSION

Increased lymphatic pressures play an important role in the pathophysiology of PLE and PB.[10,18,22,27] The albumin content of hepatic lymph is high (up to 95% of plasma).[28] In patients with raised central venous pressures, it appears that hepatoduodenal lymphatic connections become dilated and with some predisposition such as inherent structural or functional deficiencies, the normal barriers preventing leaks are broken down leading to an outpouring of this protein rich fluid into the gut.[10] The outstanding work of Itkin and Coworkers highlighted the importance of abnormal lymphatic drainage in these patients and allowed new avenues for treatment for these debilitating conditions.[9–12,17,29] Obliterating these dilated hepatoduodenal or mediastinal lymphatics may reduce the protein leak to subclinical levels.

Our results confirm that selective lymphatic embolization is feasible and effective to relieve symptoms of PLE and PB in the short term. We had patients requiring more than one embolization session, similar to Itkin et al., where 15 embolization procedures were required in eight patients.[10] In their group, three patients had a sustained improvement in serum albumin, while two had a temporary increase and in one patient albumin remained unchanged. We used a 22G Chiba needle to administer NBCA instead of the reported 27G needle with a thinner lumen.[10] It needs to be determined whether the larger bore diameter of the 22G needle and other concentrations of NBCA allow more distant and more effective administration of the embolizing agent. Also embolizing at multiple places around the portal vein targeting several periportal lymph nodes may enhance therapeutic success but also complications.

However, some patients needed an additional procedure during follow-up. This may be due to the high variability of the hepatoduodenal communications: in some patients, obliteration of only one connection had a good lasting and ongoing result; in other patients, several connections were embolized with only a temporary result and at reevaluation appearance of still other-new connections were found. This should not surprise us as the Fontan hemodynamics favor the development of new lymphatic fistulae. This technique allows to embolize only lymphatic vessels that are in close proximity to the liver hilus that carry protein-rich lymph—other more distant lymphatics can be "out of reach" for this technique.

In a patient with PB, Dori et al. cannulated the ductus thoracicus after direct transabdominal puncture of the cysterna chyli followed by selective glue embolization of the offending lymphatics.[12] Lymphatic embolization as effective treatment for PB is emphasized by a recent publication of the same group where 18 patients including children were successfully treated. We used direct transthoracic cone-beam-guided puncture of the paratracheal lymph vessels in our patient with PB as we wanted to avoid the transabdominal route as previously alluded to. Radiologists frequently use this direct puncture technique for staging of intrathoracic cancers.[25,26] Also, it avoids the need for multiple manipulations and catheters.

Some adverse events were experienced in our small group using glue embolization. This is also in agreement with the findings in the other reports; Itkin et al reported two patients who developed duodenal bleeding after Lipiodol embolization presumably due to caustic erosion of the lacteals.[10] Duodenal hemorrhage was not observed in their NBCA patients but in one out of our seven patients after a redo procedure. In two patients, small branches of the portal or hepatic veins had glue in the lumen without distal embolization nor any effect in the short term. Glue progression to the hepatic artery or vein, biliary system, or portal vein can occur and should obviously be avoided by implementing good technique. This complication may be related to either the use of the larger diameter needle, the transhepatic access, the infusion pressure, the changing viscosity, and polymerization time of the glue or as a result of the learning curve. Needle immobilization during gentle infusion is essential, and infusion must be stopped immediately if the glue follows an unexpected path (typically cranial and hepatofugal). Hepatic vein embolization, although unlikely, must be avoided as this may result in pulmonary or paradoxical cerebral emboli; fortunately, the glue is unlikely to cause a distal embolization as it remains adherent to the lymphatic cast. These patients will be followed up for the potential development of portal hypertension. Conversely, portal vein embolization has been shown to increase volume and function of remnant liver.[30,31] Other potential complications of this technique include thrombus formation, embolization to systemic vessels, creation of fistulae, local bleeding, and pain.[24,32]

We also used the same technique during this period to treat PLE in a 53-year old with severe right heart failure with the same satisfying results. Previous reports have documented success in other conditions in adults such as ascites and hepatic lymphorrhea.[23,24,31,33,34] This is not unexpected as the same basic pathophysiological pathways are shared and has the implication that the use of the percutaneous lymphatic embolization technique could be expanded to treat other causes of PLE, PB, and chylothorax.[13,14]

We did not perform extensive preprocedural imaging but especially for PB imaging techniques such as inguinal node lymphangiography and dynamic contrast enhanced magnetic resonance lymphangiography may assist in planning and selecting ideal patients for selective lymphatic duct embolization.[35–37]

4.1 | Limitations

Our numbers are limited and follow-up is limited, but this can be expected in a rare disease when embarking on novel treatments. Extensive lymphangiography was not used and may be useful to demonstrate all the areas to be treated, thereby avoiding multiple procedures. A number of questions remain unanswered, for example, for how long would these benefits be sustained as the high central venous pressure will persist and would it respond to multiple re-embolizations? Late complications are possible, for example, what is the long-term effect of NBCA on the lymphatics and the liver itself? Furthermore, validated measures of success are not clearly defined. It is evident that further research into the pathophysiology of lymphatic sequelae and treatment is essential. However, the authors are of the opinion that improvement in quality of life following this treatment in patients suffering from these debilitating conditions should not deter clinicians from exploring this novel treatment option.[38] The question is open whether glue embolization should be offered earlier instead of waiting for standard treatment options to fail in these patients.

5 | CONCLUSION

Selective embolization of dilated periportal/peritracheal lymphatics is a promising technique in Fontan patients with PLE or PB. Larger series are required to determine incidence and reasons for success/failure, with long-term results and effects on liver function. We expect this technique to rapidly outclass several other treatments.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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