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Protein-Losing Enteropathy after Fontan Procedure

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Abstract

Objectives: We reviewed the incidence, haemodynamics, treatment strategies and outcome of patients with protein-losing enteropathy (PLE) after Fontan procedure. **Methods:** The clinical records of 114 patients who underwent Fontan-type operation between 1982 and 1999 were reviewed. The cardiac diagnoses, haemodynamics, clinical presentation, treatment and outcome of those complicated by PLE, as defined by clinical evidence of fluid retention, hypoalbuminaemia (<25 g/L) and enteric loss of protein, were noted. **Results:** There were 15 early and five late deaths after the Fontan procedure. Three patients defaulted follow-up. Of the remaining 91 patients, five (5.5%) developed PLE. The median age at Fontan operation was 6.4 years (range 1.4 to 15.1). The median age at diagnosis of PLE was 10.9 years (range 6.7 to 19.2), while the median interval between surgery and diagnosis was 4.2 years (range 3 months to 9.5 years). Clinical presentations included oedema (100%), pleural effusion (60%), pericardial effusion (60%), and diarrhoea (20%). Cardiac catheterization revealed an unobstructed Fontan circuit in all of the patients, a mean (± SD) pulmonary arterial pressure of 18±4.8 mmHg (>15 mmHg in three patients), ventricular dysfunction in two patients, and mild prosthetic atrioventricular valve regurgitation in one. Medical treatment with either steroid or heparin resulted in symptomatic improvement in two patients and death in one. Blade atrial septostomy and balloon dilation of the atrial fenestration was performed in two which resulted in normalization of the albumin level in one and death in the other. **Conclusion:** Protein-losing enteropathy, though relatively uncommon after Fontan operation, is difficult to manage and is associated with morbidity and mortality. An 'optimal' post Fontan haemodynamic is not risk free of PLE.

Key words Fontan procedure; Protein-losing enteropathy

Introduction

Since the introduction of the Fontan procedure in 1971, performed in a 12-year-old child with tricuspid atresia,[1] this procedure has been applied to more complex cyanotic congenital heart diseases with a single functional ventricular chamber. The principle of the original Fontan procedure and its subsequent modifications is to direct systemic venous blood into the pulmonary circulation, thereby separating the systemic from the pulmonary venous return. The pulmonary venous return is directed to the functional single ventricle that pumps the fully oxygenated blood into the aorta. This proves, however, to be more of a palliative rather than curative procedure. Mid- and long-term complications have increasingly been recognized, which include cardiac arrhythmia,[2] diastolic cardiac dysfunction,[3] liver fibrosis,[4] coagulation factor abnormalities that predispose to thrombosis[5] and protein-losing enteropathy (PLE).[6-9]

Among the various complications, PLE appears to be one of the most difficult complications to manage once it develops. Protein-losing enteropathy, occurring in 4 to13%

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of patients 0.1 to 16.4 years after Fontan procedure,[6,7,9] is thought to result mainly from chronically elevated systemic venous pressure causing intestinal lymphangiectasia with consequent enteric loss of protein. Apart from dietary manipulation and intermittent intravenous albumin infusion, definitive treatment remains uncertain.

Fontan procedure was first performed in Hong Kong in 1982.[10] A total of 114 patients with complex cyanotic congenital heart disease has since then undergone the operation. In this study, we reviewed the incidence, haemodynamics, treatment strategies and outcome of our patients who developed PLE after the Fontan procedure.

Methods

This was a retrospective review of all patients who underwent the Fontan-type procedures between 1982 and 1999 in Grantham Hospital, Hong Kong. Those who developed PLE were identified. The diagnosis of PLE was based on the presence of fluid retention as evident clinically (dependent oedema, effusions), hypoalbuminaemia (<25 g/L), and enteric protein loss. Enteric protein loss was established by technetium 99m-labeled human serum albumin scintigraphy.[11] Other causes of hypoproteinaemia were excluded.

The clinical records of patients who developed PLE were reviewed. Their cardiac diagnosis, age at surgery and development of PLE, clinical presentations, treatment modalities and short-term outcome were reviewed. The current status of the patients in terms of symptoms and medications were noted. All of these patients had undergone cardiac catheterization upon diagnosis of PLE, and the angiographic findings and haemodynamic data were retrieved. Their systemic ventricular function and the presence of atrio-ventricular valve regurgitation were evaluated by transthoracic echocardiography.

Results

Prevalence of PLE

A total of 114 patients underwent Fontan-type procedures in this 18-year period. Of these, 15 died within two months of surgery. There were five late deaths, including two sudden deaths of unknown cause, two deaths related to end-stage cardiac failure, and one infective endocarditis. Three patients defaulted follow up. Of the remaining 91 patients, five were complicated by PLE, accounting for a prevalence of 5.5%.

Clinical Data

The cardiac anatomy of the five patients with PLE included pulmonary atresia with intact ventricular septum that occurred in two and one each of tricuspid atresia with pulmonary atresia, mitral atresia with double-outlet right ventricle, and a double-outlet right ventricle with pulmonary stenosis. The clinical data are summarized in Table 1.

The median age at Fontan operation was 6.4 years (range 1.4 to 15.1). The median age at diagnosis of PLE was 10.9 years (range 6.7 to 19.2) with a median time interval between surgery and onset of PLE 4.2 years (range 3 months to 9.5 years). The initial clinical presentation included peripheral oedema in all of the patients, pleural effusion and pericardial effusion in three (60%), and diarrhoea in one (20%).

Haemodynamic Data

All of the five patients had cardiac catheterization performed within three months of diagnosis. None had evidence of Fontan circuit obstruction. Their mean (±SD) pulmonary pressure was 18±4.8 mmHg. The mean pulmonary arterial pressure was greater than 15 mmHg (a value of 15 mmHg is regarded as optimum for a functional Fontan circuit) in three patients (patients 1, 2 and 3). Patient 3 had poor systemic ventricular function and severe atrio-ventricular valve regurgitation, for which prosthetic valve replacement was performed prior to development of PLE. The other four patients had satisfactory ventricular function with no significant atrio-ventricular valve regurgitation. Patient 4 had atrial arrhythmia for which he was started on sotalol with fair control.

Treatment and Outcomes

Antifailure Treatment

All of the patients were started on diuretics (frusemide and spironolactone) and a vasodilator (captopril) to optimize cardiac function and by reducing preload and afterload, respectively. Four patients were also given digoxin. Despite these medications, significant fluid retention persisted. Intermittent intravenous albumin infusions were required for symptomatic relief. Two patients (patients 1 and 2) who had an elevated pulmonary arterial pressure underwent blade atrial septostomy. Newer and less invasive treatment

Table 1 Clinical data of the patients with protein-losing enteropathy

Patient	Cardiac diagnosis	Age at Fontan operation (years)	Age at onset of PLE (years)	Interval between operation and PLE (years)	Clinical presentation	mean PAP (mmHg)
1	PAIVS	4.9	7	2.1	ankle oedema, pericardial effusion, pleural effusion, hepatomegaly, diarrhoea	18
2	PAIVS	1.4	10.9	9.5	ankle oedema, ascites, hepatomegaly	20
3	DORV, MA	15.1	19.3	4.2	ankle oedema, ascites, pleural effusion, hepatomegaly	18
4	TA, PA	13	17.3	4.3	ankle oedema, pericardial effusion, pleural effusion	8
5	DORV, PS	6.4	6.7	0.3	ascites, pleural effusion, pericardial effusion, hepatomegaly, hydrocele	12

Abbreviations: DORV, double-outlet right ventricle; MA, mitral atresia; PA, pulmonary atresia; PAIVS, pulmonary atresia with intact ventricular septum; PAP, pulmonary arterial pressure; PS, pulmonary stenosis; TA, tricuspid atresia

modalities including oral steroid[12-14] and subcutaneous heparin[15,16] were tried in the remaining three patients.

Blade Atrial Septostomy

Patient 1 had an elevated mean pulmonary pressure of 18 mmHg and underwent three attempts of blade atrial septostomy with balloon dilation of the fenestration at eight years of age (Figure 1). The atrial fenestration created in the initial two attempts was inadequate for decompression of the systemic venous compartment. The third attempt eventually resulted in satisfactory reduction of the mean inter-atrial pressure gradient from 10 to 5 mmHg. The albumin level increased from 15 to 28 g/dL within two months of the procedure and became normalized on follow-up. Apart from a mild lowering of the systemic oxygen saturation from 95% to 89% in room air, the problem of fluid accumulation resolved completely and the patient enjoyed satisfactory exercise tolerance with improvement of his NYHA functional class status from III to II.

Patient 2 had similarly a high mean pulmonary arterial pressure of 20 mmHg and a grossly dilated right atrium. Transcatheter fenestration of the inter-atrial septum was attempted within one month of diagnosis of PLE. The procedure was however complicated by severe hypoxaemia and cardiac arrhythmias. Atrial flutter followed by complete heart block occurred immediately after the procedure and resulted in low cardiac output and worsening of hypoxaemia. The terminal event was ventricular fibrillation that was refractory to resuscitation.

Steroid

Patient 3 had a poor haemodynamic status with impaired ventricular contractility, moderate degree of paravalvar leak despite prosthetic valve replacement and an elevated mean pulmonary arterial pressure of 18 mmHg. Surgical and catheterization interventions were considered extremely risky in view of the poor haemodynamic status. A course of intravenous methylprednisolone (dose equivalent of 1 mg/kg/day of prednisolone) was tried without response, but instead resulted in increasing fluid retention, low grade Pseudomonas vesicularis peritonitis and Legionella pneumophila pneumonia and bacteraemia, the clinical details of which has recently been reported.[17] Despite successful antibiotic treatment of his infections, this patient eventually died of refractory cardiac failure one year since the onset of PLE.

In contrast, patient 4 who had a significantly better haemodynamic status responded to steroid therapy. Although he developed episodes of atrial tachycardia and flutter that could only be partially controlled by sotalol, cardiac catheterization revealed a non-obstructed Fontan circuit, low mean pulmonary arterial pressure and

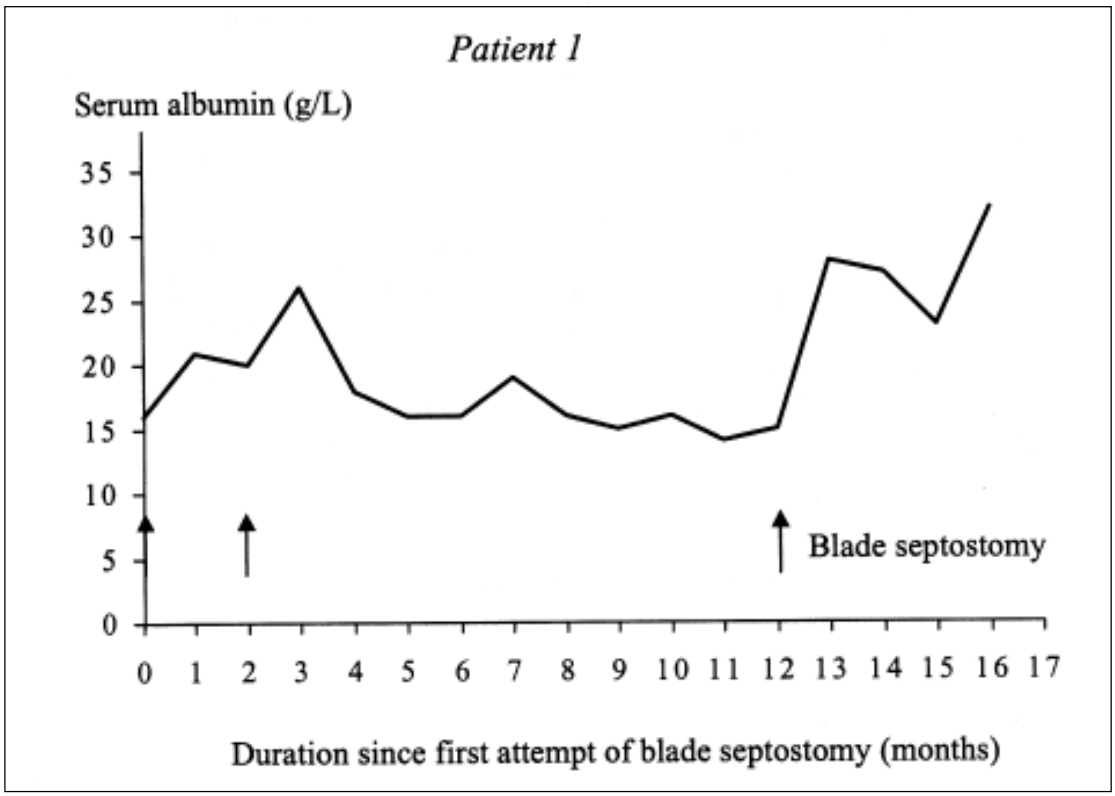

Figure 1 Changes in serum albumin level after three attempts of blade atrioseptostomy.

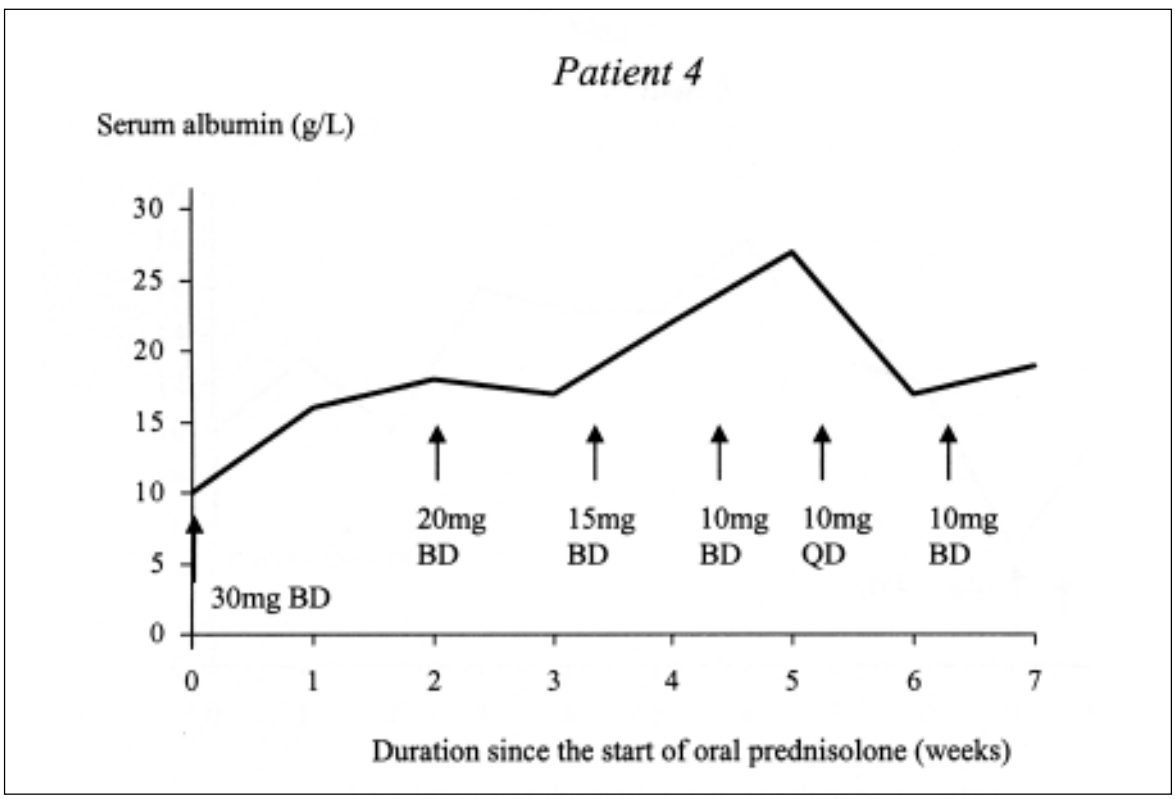

Figure 2 Increase in serum albumin level after oral prednisolone therapy.

satisfactory ventricular contractility. Oral prednisolone was started at a dose of 1 mg/kg/day with clinical improvement and gradual increase in serum albumin level (Figure 2). There were no significant complications of steroid therapy apart from a cushingnoid appearance. The prednisolone dose could gradually be decreased to a daily maintenance dose of 0.3 mg/kg/day (10 mg twice daily). The albumin level reached 39 g/L after 10 months of steroid therapy. He suffered from a minor stroke 10 months after starting steroid that was related probably to his atrial arrhythmia, but with almost complete recovery.

Heparin

Patient 5 underwent Fontan operation in Mainland China. He developed PLE at three months post operation and responded to a short course of oral steroid. He presented to us at four years after the operation with bilateral ankle oedema, pericardial effusion and pleural effusion. Cardiac catheterization in Hong Kong revealed a mean pulmonary arterial pressure of 12 mmHg, an unobstructed Fontan circuit, satisfactory ventricular contractility and absence of significant atrioventricular valve regurgitation. As the patient was worried by the side effects of steroid, daily subcutaneous injection of high molecular weight heparin at a dose of 5000 units/m^2 was tried (Figure 3). The initial encouraging response was, however, transient. Oral prednisolone was eventually restarted after a trial of heparin for nine weeks. His albumin level increased to 30 g/L 10 months later while maintained on 0.4 mg/kg/day of prednisolone.

Discussion

It is obvious even from this small case series that protein-losing enteropathy, though relatively uncommon after Fontan operation, is difficult to manage and is associated with morbidity and mortality. The five-year survival after the diagnosis of PLE has been reported to be 46%.[7] Furthermore, an optimum post Fontan haemodynamic status, in terms of a low pulmonary arterial pressure (mean 15 mmHg), a patent Fontan circuit, satisfactory systemic ventricular contraction and absence of significant atrio-ventricular valve regurgitation, is not risk free of PLE.

The small number of patients with PLE in this cohort of post Fontan patients limits detail analysis of potential risk factors predisposing to development of PLE and assessment

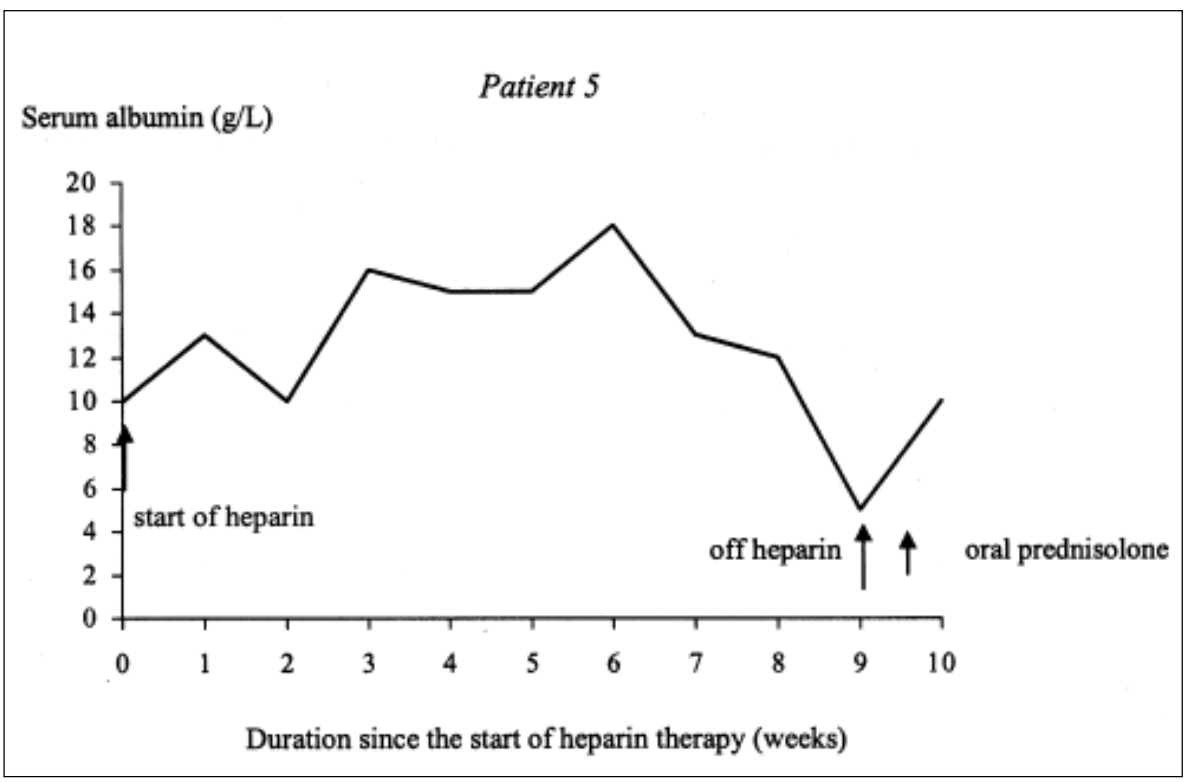

Figure 3 Transient effect of subcutaneous high-molecular weight heparin on serum albumin level.

of the efficacy of various treatment modalities. We have therefore not attempted to compare the anatomic variables or haemodynamic data of patients with PLE to those without. It is expected that an increasing number of our patients would potentially develop this complication as the incidence exceeds 10% in a number of series[6,7] and furthermore, the risk of its development increases over time.[7] Driscoll et al reported a 7-10% incidence of hypoproteinaemia in 352 survivors of Fontan procedure,[6] while Feldt et al estimated that the chance of PLE development among 30-day survivors was 13.4% by 10 years of follow-up.[7] This review of our initial experience, albeit limited, should hopefully provide us with some insight in the management strategies for subsequent patients.

Understanding of the underlying pathophysiology is crucial for effective treatment. Protein-losing enteropathy is thought to result mainly from chronically elevated systemic venous pressure that occurs after Fontan procedure and causes intestinal lymphangiectasia with consequent enteric loss of protein.[7,8] Nevertheless, an acceptable systemic venous pressure of 15 mmHg could still be associated with PLE, as illustrated in this and other reports.[9,12] Furthermore, the clinical responses to steroid[12-14] and heparin[15,16] do suggest alternative underlying mechanisms as abnormal intestinal inflammatory reaction or disturbed intestinal glycosaminoglycans production that remain to be unveiled. A definitive treatment is hence unavailable and standard dietary manipulations and intermittent albumin infusions appear to be of limited use.

For patients with an elevated systemic venous pressure, the first logical step would probably be optimization of the Fontan circuit by eliminating distal pulmonary arterial obstruction, either by balloon angioplasty or stent implantation. Decompression of systemic venous system by either surgical[18] or transcatheter creation of an atrial fenestration[9] may reduce systemic venous pressure and amelioration of PLE symptoms, although at the expense of a right-to-left intracardiac shunt, resulting in systemic arterial oxygen desaturation and increased risk of systemic thromboembolism.[9] Furthermore, puncture of the interatrial septum is not without risk and that repeated transcatheter interventions might be required as illustrated in two of our patients. Likewise, the risk of surgery is high with a reported mortality of 62 to 75%,[7,9] attributed in part to prolonged duration of cardiac failure and the catabolic state. It is noteworthy, however, that an adequate atrial fenestration does not guarantee complete resolution of PLE.[9]

In the absence of systemic venous hypertension, corticosteroids have been used with success.[7,9,12-14,19] Long term benefits with complete remission had been achieved in 12 of the 32 reported patients, partial benefit in 11 and no benefit in nine. The mechanism of action, as alluded to earlier, remains unclear. It has been postulated that steroid may stabilize intestinal capillary and lymphatic membranes through its anti-inflammatory effect.[13] The potential benefit of steroid, however, must be weighed against its side effects. Secondary to the impairment of lymphatic drainage in PLE, lymphocytes and immunoglobulins leaked into the intestinal lumen.[12,20] Muller et al further demonstrated that the lymphocyte population predominantly reduced in PLE was that of $CD3^+$ and $CD4^+$.[21] Hence, quantitative impairment of both humoral and cell-mediated immunity is present in this group of patients. Institution of steroid may further predispose the patients to infections as illustrated in patient 3.[17] Although the use of steroid therapy in protein-losing enteropathy seems promising, this treatment modality should be used sparingly and with caution. Furthermore, the effectiveness of steroid in the presence high systemic venous pressure remains to be determined.

The recent reports of success of subcutaneous high-molecular-weight heparin therapy were limited to a small number of patients, with response shown after three weeks to six months of treatment.[15,16] Our patient, however, did not show a lasting response to heparin despite nine weeks of treatment. The exact mechanism is similarly unclear. Heparin sulfate, which is a component of basement membranes, might become incorporated into endothelial cells to stabilize the capillary endothelium and reduce protein leak into the extravascular space and gut. The failure rate of this treatment modality is still unknown and the total duration of treatment in those who respond remains to be determined.

Undoubtedly, further studies are warranted to unveil alternative mechanisms, apart from chronic venous congestion, leading to PLE in post Fontan patient for targeted treatment modalities. It remains to be determined whether newer surgical modifications of the Fontan circuit that aim to improve systemic venous flow dynamics would reduce the prevalence of PLE.

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