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Review

Protein-losing enteropathy after Fontan operation

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Summary. Protein-losing enteropathy (PLE) is a rare but severe complication of Fontan operation with high mortality and recurrent rates. It often develops 1-9 years after Fontan operation. This disorder often leads to chronic malnutrition, global immune dysfunction and failure to thrive in addition to peripheral edemas. PLE is often associated with increased chronic inflammatory biomarkers, such as C-reactive protein, complement fragments and tumor necrosis factor-α, etc., and decreased acute inflammatory biomarkers, for instance, lymphocytes. Abnormal fecal α_1-antitrypsin clearance is the golden diagnostic standard of PLE. The management strategies include medical, surgical and interventional therapies. However, none of the proposed treatment shows a specific efficacy to PLE after Fontan operation. Management of choice for PLE relies on the substantial response of the patient to the underlying regimen, and the patients may eventually warrant heart transplantation. The PLE-related mortality is high with cardiac dysfunction, severe infection and multiorgan failure being the major causes of death. Attempts to diminish Fontan failure and seek for effective therapeutic regimen for PLE after Fontan operation are research works of next step.

Key words: alpha 1-antitrypsin, Fontan procedure, protein-losing enteropathies

Introduction

Erosive and non-erosive gastrointestinal disease and increased interstitial pressure can be the underlying causes of protein-losing enteropathy (PLE). It has been recognized that a number of cardiac diseases may also lead to PLE (1). The most frequent cardiac cause of PLE is Fontan operation. The Fontan procedure is performed for the patients with a functional single ventricle by restructure the heart to allow supplying enough blood to the pulmonary circulation (1).

PLE is a rare but severe complication of Fontan operation with a very high mortality rate, and reoccurrence is also frequent (2). In a multicenter retrospective study including 3,029 Fontan operations, the incidence of PLE in the survivors was 3.7% and the incidence of PLE relative to the total number of Fontan operations in each center varied between 0% and 25% (3). In subsequent clinical studies with smaller patient populations, the incidence of PLE after Fontan operation was 5.5-12% (4, 5). The mechanisms of PLE after Fontan operation are poorly understood, and all the proposed therapeutic regimens only obtained limited success. In order to discuss the disputes over the PLE after Fontan operation, a review is made herewith.

Time of onset

Pundi *et al*. (6) reported that the mean age of patients at Fontan operation was 11.2 ± 8 years and the mean interval from Fontan operation to the diagnosis of PLE was 8.1 ± 7.9 years. Yu *et al*. (7) described that the median interval from Fontan operation to PLE development was 2.2 years. Factors relating to the time of PLE development based on univariate analysis were pulmonary vascular compliance, postoperative central venous pressure, and durations of Intensive Care Unit

stay, hospitalization and chest tube indwelling, whereas multivariate analysis showed that only pulmonary vascular compliance remained significant (7). Pundi *et al*. (6) reported that the mean interval from Fontan operation to onset of PLE by types of Fontan was 9.0 ± 8.7 years for atriopulmonary connections, 6.5 ± 4.7 years for lateral tunnels, 4.9 ± 3.1 years for extracardiac conduits and 6.6 ± 8.7 years for other types of Fontan operation. As reported by Lin *et al*. (5), the interval was 4.3 ± 3.4 (range, 1.3-9.4) years for atriopulmonary anastomosis in six patients, 6.4 and 9.7 years for two patients with lateral tunnel total cavopulmonary connection and 1.2 years for a single case of Kreutzer procedure.

Clinical manifestations

Most frequently, the onset of PLE is heralded by a new onset of pleural effusion, ascites, or peripheral edema (8). Most patients had edema (79%) and effusions (75%) (3). In PLE, protein requirements may increase to 2.0-3.0 g/kg/day to achieve positive protein balance in comparison to a normal requirement of 0.6-0.8 g/kg/day (1).

Ostrow *et al*. (9) reported that over one-third of the patients showed elevation of inflammatory markers including tumor necrosis factor-α and C-reactive protein (9). Rychik (10) observed that C-reactive protein was >1 mg/dL in 35% and >3 mg/dL in 16% of all patients with PLE after Fontan operation. Table 1 shows biomarker changes in this patient setting.

Although C-reactive protein, tumor necrosis factor-α, brain natriuretic peptide and angiotensin II levels were elevated; however, they had no correlation with abnormal enteric protein loss (9). Instead, there might be a severe decrease of $CD4^+$ lymphocytes (16). Apparent selective loss of $CD4^+$ lymphocytes could lead to reversal of the CD4/CD8 ratio (12).

Mechanisms

Impaired protein glycosylation may contribute to PLE. Patients with a deficiency in phosphomannose isomerase had periodic PLE, which could be resolved when glycosylation disorders were handled properly by daily supplements of mannose (17).

Several immunological alterations of such patients after PLE are similar to those found in patients with PLE of other etiologies. Muller *et al*. (18) reported the preferential loss of $CD3^+$ and $CD4^+$ cells into the gastrointestinal tract in patients with constrictive

Table 1. Biomarker changes in patients with protein losing enteropathy after Fontan operation

Change	Biomarker	
	Blood/serum (9-14)	**Intestinal mucosa (15)**
Decreased	Protein, γ-globulin & immunoglobulin G; Lymphocyte count; $CD4^+$ lymphocytes; CD4/CD8 ratio; Thyroid stimulating hormone	
Increased	α_1-globulin, α_2-globulin & β-globulin; Neutrophil; Natural killer cells; C-reactive protein; Complement fragment C3d; Tumor necrosis factor-α; Brain natriuretic peptide; Angiotensin II; Interleukin-8	Interferon-γ

pericarditis. PLE after total cavopulmonary connection was associated with areduced immunoglobulin G production, which was possibly a result of reduced B cell differentiation or the absence of costimulatory T helper cells. However, B cells of PLE patients may still be stimulated to produce immunoglobulin G as evidenced by *in vivo* corticoid administration (19). The passive lymph loss secondary to an increased central venous pressure could not explain the selective loss of $CD4^+$ lymphocytes, suggesting that the disturbance of the immune system could initiate local cytokine network disturbance of the gut and perturbe its homeostasis and immune defense. This process could affect the structural integrity and patency of the intestinal wall, thus triggering PLE (16). As already observed, PLE after total cavopulmonary connection was accompanied by signs of an acute inflammatory response and a dramatic loss of T cells, in particular of the αβ TCR^+ $CD4^+$ subtype (13).

Chronic venous congestion causes the lymphatics to decompress into the pleural or abdomen cavity. Under such circumstances, loss of proteins and lymphocytes and an inflammatory response leads to chronic malnutrition (20). Some authors suggested that mesenteric hypoperfusion would be a possible trigger for the development of the PLE as a result of an increased mesenteric vascular resistance (21). The pathophysiology of PLE after Fontan operation and its sequelae are shown in Figures 1 and 2 (9-11, 22). In general, factors leading to impairment to the enteric immune defense system might serve as a trigger of PLE (11).

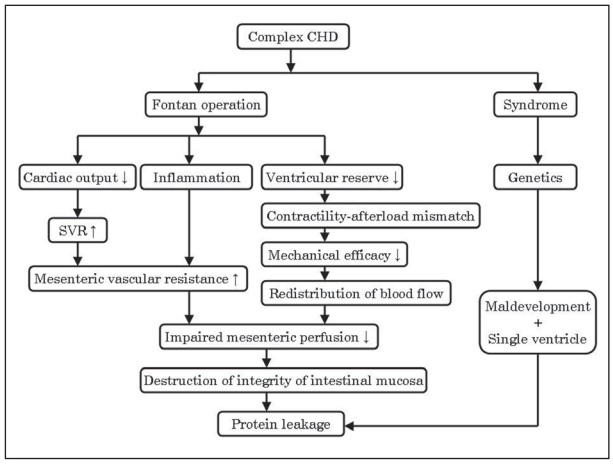

Figure 1. The pathophysiology of protein-losing enteropathy after Fontan operation. CHD: congenital heart defect; SVR: systemic vascular resistance.

Risk factors

Perioperative factors associated with development of PLE included longer cardiopulmonary bypass time, increased left atrial pressure after the operation, longer length of hospital stay, and presence of postoperative renal failure (8). It is possible that the association between infection and PLE might be a manifestation of an impaired immune system during the early development of PLE, rather than a causal factor (11).

In fact, several issues may be related to the occurrence of PLE and these may include pulmonary artery stenosis, Fontan conduit stenosis, major systemic-to-pulmonary artery collaterals, residual significant pulmonary forward flow, single ventricle dysfunction and atrio-ventricular valve dysfunction (23).

Diagnosis

The gold standard test for diagnosis of PLE is an abnormal fecal α_1-antitrypsin clearance (24). Normal α_1-antitrypsin clearance is typically <30 mL cleared/24 hours. Single spot analysis of stool concentration of α_1-antitrypsin values exhibited a correlation with the clearance values and could be used for the diagnosis of PLE in the absence of a 24-hour stool collection (25). The cut-off values of fecal α_1-antitrypsin clearance and fecal α_1-antitrypsin concentration were defined as >27 mL/24 hours and >54 mg/dL, respectively (25). The diagnostic criteria for PLE were, serum albumin level <3 g/dL, total protein <5 g/dL and elevated stool α_1-

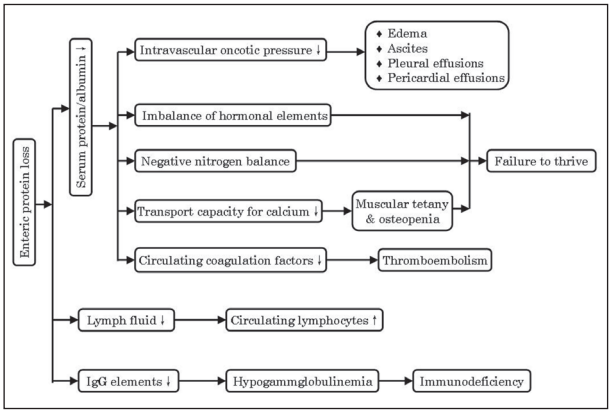

Figure 2. The sequelae of protein-losing enteropathy after Fontan operation. IgG: immunoglobulin G.

antitrypsin clearance (26). Besides, lymphangiectasia could be noted in patients undergoing gastric and small-bowel biopsies (11, 26). Bidirectional endoscopy could be applied for random biopsies of the duodenum and colon (1). Lymphangiectasia of the intestinal tract secondary to lymphatic hypertension could frequently be disclosed in PLE patients (6).

Treatment

Medical management

Supportive treatment: The current medical management of PLE consists of diet modification, albumin and (or) γ-globulin infusion, diuretics and corticosteroids, none of which have been entirely successful. The use of intermittent intravenous infusions of albumin is generally unhelpful in the long run (1). Anti-inflammatory therapy can at least temporarily reduce tumor necrosis factor-α levels (27).

Heparin: Substitution of heparin can reverse protein loss by protecting the intact cellular membrane of the intestinal mucosa (27). Recently, heparin therapy was reported to improve symptoms of PLE patients and essentially prevent enteric protein loss within 3 weeks of administration (28), so was a high dose subcutaneously unfractionated heparin (25,000 units/day) in addition to warfarin (12). Long-lasting relief has been reported by systemic administration of unfractionated heparin, but induction of severe osteoporosis may limit its long-term use (29). Intravenous heparin may be useful to decrease fluid secretion and protein exudation from the bowel.

Prednisolone: Prednisolone 2 mg/kg/day in children, or 25-60 mg twice a day in adolescent patients with a slow tapering regimen over five to six months is a preferred regimen (30). The membrane stabilizing effect of prednisone leads to a rapid cessation of enteric protein loss from the gut and the peripheral vasculature, with quick subsidence of a swelling with subsequent recovery of albumin and protein concentrations (30).

Octreotide: Patients with PLE after Fontan operation received intramuscular octreotide therapy (10-20 mg/month) for a period of 14-28 months have achieved a promising effect by symptomatic improvement and significantly reduced serum albumin, total protein and α_1-antitrypsin levels (31, 32). However, the mechanism of this drug in treating PLE is poorly understood and warrant further elaborations.

Sildenafil: The effect of sildenafil is likely to be due to a combination of actions including a reduction of pulmonary vascular resistance, dilating the mesenteric vessels and increasing mesenteric arterial flow (33). In a pediatric patient with PLE after Fontan operation, a trial of sildenafil at 0.5 mg/kg/dose, 4 times a day, with a rapid increase to a maximum of 1.5 mg/kg/dose was given. Her fecal α_1-antitrypsin levels returned to a normal value 6 weeks after oral sildenafil treatment (33). Maeda *et al*. (34) prescribed sildenafil in 3 young patients who underwent total cavopulmonary connection for single ventricle or double outlet right ventricle at a dose of 30 mg/day or 0.5-1 mg/kg/day titrating up to 4-8 mg/kg/day. Ascites in the patients were eventually resolved.

Budesonide: John *et al*. (35) reported treatment with controlled release budesonide was started at 9 mg daily for all patients with PLE after Fontan operation. The dose in 5 patients was weaned within 6-9 months to 3 mg daily or 3 mg every other day. The effect time was 6 months for serum albumin recovery or symptomatic improvement after the start of therapy. However, side effects of oral budesonide may limit its clinical use. Therefore, one must take caution with the use of this drug, and weaning and discontinuation is indicated if severe side effects are noted within 3-6 months.

Spironolactone: Spironolactone, a nonselective aldosterone receptor antagonist, has become an important adjuvant therapy for treatment of congestive cardiomyopathy. Ringel and Peddy (29) applied a high-dose spironolactone in three children who developed PLE after Fontan operation and achieved remission.

Surgical treatment

Fenestration: Late fenestration is an effective means of alleviating serious morbidity from effusions or PLE after Fontan operation. Fenestration of the interatrial septum should be considered in patients with a poor clinical result after Fontan operation, before proceeding to Fontan take-down or heart transplanta-

tion. Fenestration techniques included blade/balloon septostomy, stent placement, Amplatzer-fenestrated atrial septal defect device and balloon dilation of previous stent. Vyas *et al*. (36) reported that the size of the fenestration that they created was 5.2 ± 1.1 mm. After fenestration, cardiac index increased significantly, and reduction of ascites and edema was noted after 9 of the 16 procedures. Rychik *et al.* (26) reported that late creation of a surgical fenestration was performed in 9 patients, with 5 of them being PLE after lateral tunnel-type Fontan operation, and 3 having normalization of serum proteins and resolution of symptoms at 2-6 weeks. They also noted the relation between resolution of symptoms and the extent of right-to-left shunt created.

Fontan revision: Fontan revision should be considered for the patients with a previous atrio-pulmonary Fontan. In this way, a more conventional, more streamlined and energy efficient, extracardiac conduit-type Fontan is constructed. Theoretically, such patients have improved hemodynamics and increased cardiac output after a Fontan revision (37).

Intestinal resection: Resection of affected segments in lymphangiectasia may control symptoms and intestinal protein loss, and the serum proteins and immunoglobulins stabilized (38). Connor *et al*. (31) performed ^{99m}technetium-dextran scintigraphy to assess the extent of intestinal protein loss and a resection of localized intestinal lymphangiectasia was performed in a 14-year-old girl. She has remained well postoperatively, with normal bowel habit and no evidence of short bowel syndrome, reaccumulation of ascites, or pleural effusions.

Interventional procedures

Percutaneous fenestration: Mertens *et al*. (3) reported that three types of interventional procedures were performed in 13 patients with PLE: a balloon dilation with or without stenting of a stenosis on the Fontan-type connection or of a stenosis on the pulmonary artery (*n*=9), percutaneously creating a fenestration in the intraatrial septum (*n*=5) and systemic–pulmonary artery collateral occluded with coils (*n*=1). A marked effect was observed on the PLE symptoms in most of these patients.

Atrial pacing: In patients with post-Fontan PLE with sinus node dysfunction, complete resolution of PLE was observed within three weeks of placement of an epicardial single-chamber pacemaker. This result heralded that atrial pacing could be an alternative treatment regimen for patients with PLE after Fontan operation (39).

Prognosis

The prognosis of patients with PLE after Fontan operation has been improved steadily. A retrospective study on a large patient population revealed that the 10-year survival of these patients was 77% (40). Pundi *et al*. (6) reported that the overall mortality in the PLE cohort was 72% over 7 ± 7.4 years of follow-up, and the the overall freedom from PLE at 10, 20, and 30 years after the Fontan operation was 92%, 89% and 83%, respectively. In Fontan patients with PLE, freedom from death or the transplantation was significantly decreased compared to those without PLE (2). The death causes known in 36 patients with PLE after Fontan operation were congestive heart failure, sepsis and multiorgan failure, unrelated to PLE (6).

Conclusions

PLE is a rare but severe complication of Fontan operation with high mortality and recurrent rates. This disorder often leads to chronic malnutrition and global immune dysfunction in addition to peripheral edemas. Abnormal fecal α_1-antitrypsin clearance is the golden standard for the diagnosis of PLE. The management strategies include medical, surgical and interventional therapies. However, none of the proposed treatment show specific efficacy to some patients with PLE, and thus they may eventually warrant heart transplantation. The PLE-related mortality is high with cardiac dysfunction, severe infection and multiorgan failure being the major causes of death. Attempts to diminish Fontan failure and seek for effective therapeutic regimen for PLE after Fontan operation are research works of next step.

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