Protein-Losing Enteropathy after the Fontan Operation: Clinical Analysis of Nine Cases

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Background: Protein-losing enteropathy (PLE) is a serious complication of a Fontan operation and has a very high mortality rate. The purpose of this study was to investigate the incidence, clinical manifestations, diagnostic approaches, laboratory findings, therapeutic modalities and outcome of patients with PLE at our institution.

Methods: The diagnosis of PLE was based on clinical manifestations and laboratory studies. We reviewed medical records of patients who received a Fontan operation at our hospital form July 1985 to October 2005.

Results: A total 101 patients underwent various modifications of the Fontan procedure during this period. Nine of the 75 patients (12%) who survived 30 days after surgery developed PLE, including 4 boys and 5 girls. The median time interval between the Fontan operation and onset of PLE was 3.7 years (range 1.2 to 9.7 years). Laboratory examination showed low serum albumin levels and increased fecal α-1-antitrypsin excretion. Lymphangiectasia was found on intestinal biopsy. Six patients had cardiac catheterization after development of PLE which demonstrated an elevated mean right atrium pressure (22.5 ±6.4 mmHg, range 16 to 33 mmHg) and mean pulmonary artery pressure (22.3 ±6.4 mmHg, range 16 to 33 mmHg). Treatment included diet modification, albumin infusion, diuretics, inotropes, corticosteroids, heparin, and surgery. Four patients received medical treatment only. Two of these patients died due to sepsis and heart failure and 2 survived with partial relief of PLE. The remaining five received surgery for PLE after medical treatment failure. Three of them died after the operation and the two survivors were free of PLE, but one died of ventricular tachycardia 8 years later. The overall mortality rate was 67% (6/9).

Conclusions: The current treatment for PLE is associated with a very high mortality rate. Further investigation is needed to determine the exact mechanism of the disease and to develop new therapeutic approaches.

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Key words: protein-losing enteropathy, Fontan operation.

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Fontan surgery has been perceived as a revolutionary treatment for patients with complex congenital heart disease in whom a biventricular repair is not possible.[1,2] However, over time, a number of postoperative complications have emerged. Protein-losing enteropathy (PLE) occurs in 4% to 13% of patients following the Fontan procedure and the 5-year survival after its onset is approximately 46% to 59%.[3,4]

The exact mechanism of PLE remains unknown. Increased systemic venous pressure and subsequent disturbance in lymphatic drainage after the Fontan operation are likely to be involved.[5] A variety of treatment modalities have been tried with varying rates of success. Over the past two decades, nine cases of PLE occurred in survivors who received the Fontan operation at our institution. We report the incidence, clinical manifestations, diagnostic approaches, laboratory findings, treatment modalities and outcomes of these patients with PLE.

METHODS

We reviewed the medical records of patients who received the Fontan operation at Chang Gung Memorial Hospital from June 1985 to October 2005. The clinical data reviewed included gender, cardiac diagnosis, age at Fontan operation, type of Fontan modification, clinical manifestations, interval between the Fontan operation and the onset of PLE, follow-up period after onset of PLE, cardiac catheterization data after onset of PLE, laboratory and intestinal biopsy results, therapeutic modalities and outcome.

The diagnosis of PLE was based on clinical symptoms and laboratory studies.[3,4] The manifestations of hypoproteinemia were effusion and peripheral edema. Laboratory studies included serum albumin and total protein level, urinalysis to exclude renal protein loss, liver function test for normal protein production, fecal α-1-antitrypsin excretion f to confirm enteric protein loss and intestinal biopsy for pathologic changes. Cardiac catheterization was indicated in all patients with PLE to determine complete hemodynamic status. Because of the varied approaches to diagnosis and treatment of PLE and refusal by the patient to undergo some of the examinations, some data were not available. The numeric data are repressed either as median or mean ± standard deviation with or without a range.

RESULTS

Patient characteristics

There were 101 patients who underwent various modifications of the Fontan procedure between July 1985 and October 2005. PLE was diagnosed in nine of 75 patients (12%) who survived 30 days after the Fontan operation. All nine patients experienced some of the following clinical symptoms: puffy eyelids/ face, dyspnea, abdominal distension, diarrhea, scrotal swelling and lower leg edema.

The characteristics of these 9 patients with PLE are summarized in Table 1. The median age at

Table 1. Characteristics of 9 Patients with Protein-Losing Enteropathy

Patient	Gender	Cardiac anatomy	Fontan operation			Time interval (year)	
			Age (year)	Type	Fen	Post Fontan to PLE	Post PLE follow-up
1	M	SV, TGA	9.8	Kreutzer	no	1.2	8.3*
2	F	TA, TGA	12.3	APA	no	1.3	2.8*
3	F	TA, TGA	3.3	APA	no	2.5	8.8*
4	M	DILV, TGA	8.3	APA	no	1.4	10.2
5	F	DORV, ECD	7.6	APA	no	3.7	4.9*
6	F	SV, TGA	6.1	APA	no	7.5	6.1
7	M	SV, TGA	6.3	APA	no	9.4	3.3*
8	M	SV, TGA	4.4	TCPC	no	9.7	3.8
9	F	DILV, TGA	3.3	TCPC	no	6.4	0.2*

Abbreviations: APA: atriopulmonary anastomosis; DILV: double-inlet left ventricle; DORV: double-outlet right ventricle; ECD: endocardial cushion defect; F: female; Fen: fenestration; M: male; SV: single ventricle; TA: tricuspid atresia; TCPC: lateral tunnel total cavopulmonary connection; TGA: transposition of great arteries.

* ended follow-up when patient died.

Fontan operation was 6.3 years (range 3.3 to 12.3 years). All patients had no fenestration at the atrial level. The median time interval between the Fontan operation and the onset of PLE was 3.7 years (range 1.2 to 9.7 years). The median duration of follow-up after the diagnosis of PLE was 4.9 years (range 0.2 to 10.2 years). Six patients died during follow-up.

Laboratory examinations

Urinalysis and liver function tests were all normal in these nine patients. Low serum albumin and total protein levels were noted at the time of diagnosis of PLE. Fecal α-1-antitrypsin excretion was examined in 5 patients and the mean value was 60.8 ± 27.4 mg/g lyophilized stool (normal value: < 2.9 mg/g). Four patients had biopsies of the small intestine. Except for patient 5, the biopsies all demonstrated lymphangiectasia and increased lymphoplasma and neutrophilic cell infiltration in the lamina propria. The intestinal villi were not shortened, implying normal absorption function (Table 2).

Cardiac catheterization

The hemodynamic data are shown in Table 2. Catheterizations were performed after the onset of PLE in 6 patients. The other three refused catheterization. The mean right atrial pressures and the mean pulmonary artery pressures were significantly elevated after the Fontan operation. The mean ventricular end-diastolic pressures were not significantly different from that of normal.

Treatment and outcome

A high protein and low fat diet supplemented with medium-chain triglyceride oil was introduced to all patients. Intermittent albumin infusion and diuretics were administered for symptomatic relief. Positive inotropic agents and afterload reducing agents were used according to the patients' clinical conditions. Prednisolone was given to almost all patients after the onset of PLE. Patients 1 and 2 had early cases and prednisolone was not recommended for treatment at that time. The dose of prednisolone was 0.2 to 1.5 mg/kg/day. Subcuta-neous high molecular weight heparin injection, 5000 units per day, was tried in 2 patients (patients 3 and 5). All these medical treatment modalities showed only transient relief of PLE (Table 3).

Four patients (patients 2, 4, 5 and 6) received medical treatment only, with partial relief in 2 who still experienced PLE symptoms and needed albumin infusion intermittently. Two of the four patients died of PLE. The other five patients (patients 1, 3, 7, 8 and 9) had medical treatment for 0.2 to 8.8 years, which was unsuccessful, and then received one or more of the following surgical revisions: revision for residual hemodynamic lesions, surgical fenestration creation or conversion of atriopulmonary anastomosis (APA) to lateral tunnel total cavopulmonary connection (TCPC). Three patients died after revision

Table 2. Laboratory Examinations of 9 Patients with Protein-Losing Enteropathy

Patient	Hemodynamics after PLE (mmHg)			Alb (g/dL)	TP (g/dL)	α-1-AT (mg/g)	Bx
	RAP	PAP	VEDP				
1	23	22	8	2.9	4.2	-	-
2	16	16	6	0.9	2.8	38.1	-
3	-	-	-	1.4	3.6	75.0	+
4	25	25	12	2.4	4.2	-	-
5	-	-	-	1.8	3.4	91.4	+
6	-	-	-	1.9	3.3	-	-
7	33	33	10	2.4	4.5	-	-
8	16	16	5	2.1	3.7	80.3	+
9	22	22	5	2.2	4.6	19.3	+
Mean	22.5 ± 5.8	22.3 ± 5.8	7.7 ± 2.6	2.0 ± 0.6	3.8 ± 0.6	60.8 ± 27.4	

Abbreviations: α-1-AT: fecal α-1-antitrypsin excretion (mg/g lyophilized stool); Alb: serum albumin level; Bx: intestinal biopsy; PAP: pulmonary arterial pressure; RAP: right atrial pressure; Rp/Rs: pulmonary/systemic vascular resistance ratio; TP: serum total protein level; VEDP: ventricular end-diastolic pressure.
+ performed;
- not performed.

Table 3. Treatments and Outcomes of 9 Patients with Protein-Losing Enteropathy

Patient	Diet	Alb	D	I	P	H	Onset of PLE to revision Op (y)	Outcomes
1	+	+	+	+	-	-	0.5	Successful revision OP. Died of VT 8 years later.
2	+	+	+	+	-	-	-	Medical treatment only. Died of sepsis.
3	+	+	+	+	+	+	8.8	Died after revision, conversion and fenestration OP.
4	+	+	+	+	+	-	-	Medical treatment only. Partial relief of PLE.
5	+	+	+	+	+	+	-	Medical treatment only. Died of heart failure.
6	+	+	+	+	+	-	-	Medical treatment only. Partial relief of PLE.
7	+	+	+	+	+	-	3.3	Died after conversion and fenestration creation OP.
8	+	+	+	-	+	-	0.8	Successful OP to create fenestration.
9	+	+	+	-	+	-	0.2	Died after revision and fenestration creation OP.

Abbreviations: Alb: albumin infusion; D: diuretics; Diet: diet manipulation; H: subcutaneous heparin injection; I: inotropes and afterload reducing agents; OP: operation; P: oral prednisolone; VT: ventricular tachycardia; y: year.
+ used or performed;
- not used or performed.

surgery and the two survivors were free of PLE, but one died of ventricular tachycardia 8 years later. The overall mortality rate was 67% (6/9) (Table 3).

The catheterization examination of patient 1 showed regional narrowing at the junctional area between the right atrium and pulmonary artery although no pressure gradient could be demonstrated. Surgical relief of the suspected stenosis was performed. It revealed a fibrotic ridge at the anastomosis site. PLE resolved completely after the operation. Frequent premature atrial contractions and junctional tachycardia developed 5 years after the revision operation. Although the patient received treatment with anti-arrhythmic agents, he died of ventricular tachycardia 3 years afterwards. Patient 3 refused cardiac catheterization after the onset of PLE. Magnetic resonance imaging showed narrowing at the junctional area between the right atrium and main pulmonary artery, and at the bifurcation area of the main pulmonary artery. She underwent revision surgery for possible stenosis combined with conversion of the APA to a fenestrated lateral tunnel TCPC and died 3 days postoperatively of multiple organ failure. Patient 7 developed atrial flutter-fibrillation with a rapid ventricular rate and PLE 9.4 years after an APA type Fontan operation. There was no “focus” in the atrial flutter-fibrillation. He was treated with amiodarone successfully but PLE recurred 3.3 years later. Surgical conversion of the APA to a fenestrated lateral tunnel TCPC was unsuccessful. Patient 8 underwent successful surgical fenestration of the non-fenestrated lateral tunnel TCPC about 10 months after the onset of PLE. He was free of PLE after surgery and did not need medication during 3 years of follow-up. Patient 9 developed PLE 6.4 years after lateral tunnel TCPC, and in the meantime, residual left ventricle-to-main pulmonary artery flow and a restrictive bulboventricular foramen were diagnosed. Revision surgery for the residual lesions and surgical fenestration of the nonfenestrated lateral tunnel TCPC were unsuccessful.

DISCUSSION

Although PLE in patients with congenital heart disease who have had a Fontan operation is life-threatening, no long-term effective therapy for this condition has been developed. Initial treatment modalities for PLE include a low fat, high protein, medium-chain triglyceride diet to reduce intestinal lymphatic production and albumin infusion to increase intravascular osmotic pressure, as well as institution of diuretics, afterload reducing agents, and positive inotropic agents to lower central venous pressure. These modalities were associated with only transient relief of clinical symptoms and limited success in our patients.

Patients in this study all showed low levels of serum albumin and total protein, which may result from malnutrition, impaired synthesis or increased protein loss. All patients in this series had normal liver function tests and urinalyses, implying normal protein synthesis and no renal protein loss. But low serum albumin persisted in spite of intermittent albu-

min infusion. Enteric protein loss was documented in 5 of our patients by measuring random fecal α-1-antitrypsin, a quantified method which has shown reliable and reproducible results.[6,7] Studies also show that enteric protein loss begins before the appearance of hypoproteinemia in patients after a modified Fontan operation.[8,9]

Although the exact mechanism of PLE is not known, explanations for protein loss include the markedly increased systemic venous pressure after the Fontan procedure and subsequent impediment in lymphatic drainage.[5] Reports have demonstrated resolution of clinical symptoms of PLE after fenestration of the atrial septum in nonfenestrated patients, relief of pathway obstruction of the Fontan circulation and correction of hemodynamic lesions.[10-13] In our series, reversal of PLE was noted in patient 1 after correction of pathway stenosis and in patient 8 after surgical creation of a fenestration in the nonfenestrated lateral tunnel TCPC.

The non-laminar venous blood flow that results from the postsurgical anatomy, such as from an APA or right atrium-right ventricle conduit, may cause energy loss and may also result in low cardiac output and development of symptoms.[14,15] Conversion of an APA to a lateral tunnel or extracardiac TCPC results in improvement in exercise ability and arrhythmias. But it has shown varying effects on PLE, from no improvement to significant amelioration.[16-19] Heart transplantation is also a consideration for PLE, particularly if ventricular dysfunction is present.[20] However, surgery in patients with PLE is associated with a very high mortality rate. An international multicenter study showed a surgical mortality rate of 61.6%.[4] In our patients, five had surgery for PLE and three of them died after the operation.

Much lower surgical mortality rates after Fontan conversion have been reported in the literature. Kreutzer and coworkers reported 1 death in 8 patients who received conversion to lateral tunnel TCPC for various complications of APA.[16] More recently, Weinstein and associates reported 2 deaths in 10 patients and Marcelletti and colleagues demonstrated 3 deaths in 31 patients who underwent extracardiac conversion for complications after a previous Fontan operation.[18,19] However, only 7 of the 49 patients in these 3 series had PLE. PLE was regarded as a serious complication in these studies and, in Kreutzer's study, it received the same clinical score as patients who had class III or IV congestive heart failure (New York Heart Association classification). In addition, the *mean right atrial pressure of our PLE patients was higher than those of the patients in these 3 series. The mean (+ SD) right atrial pressures in mmHg, were 18.3±4.6, 15.3±4.8 and 15.2 (no SD reported) for Kreutzer's series, Weinstein's series and Marcelletti's series, respectively. But the right atrial pressure was 23.5±5.8 in the 4 patients (patients 1, 7, 8, and 9) who had catheterization and revision surgery for PLE in our series. Our higher failure rate after surgical intervention may have been due to the unfavorable hemodynamics of our patients, the fact that all our patients had PLE, or the small number of patients in our study.

Atrial arrhythmias are a late complication of the Fontan operation, especially in the APA modification.[21,22] A junctional rhythm and loss of atrioventricular synchrony can have deleterious effects on Fontan physiology by diminishing cardiac output. Cohen and associates reported improvement in symptoms of PLE after atrial pacing.[23] In our patient 7, there was no "focus" in atrial flutter-fibrillation. With amiodarone treatment, he experienced clinical improvement but the symptoms recurred 3.3 years afterward.

Lymphangiectasia of the intestinal tract secondary to lymphatic hypertension is noted frequently in PLE. Dilated lacteals may leak contents such as albumin, immunoglobulin and lymphocytes into the intestinal lumen.[24,25] Autoimmune processes may also contribute to the pathogenesis of PLE and diseases such as systemic lupus erythematosus may present with severe protein loss. There are reports of responses to corticosteroids and immunosuppression.[26,27] Corticosteroid therapy for PLE after a Fontan procedure was first reported in 1991.[24] The mechanism of action of corticosteroids in the treatment of PLE is unclear. Whether the action is through the anti-inflammatory properties or the cellular anabolic effect of steroids is unknown.[24] Prednisolone therapy for PLE was administered to almost all in our patients., This treatment showed obvious effects at the beginning but these effects declined later. To our knowledge, the causes of the declined effect of prednisolone for PLE also have not been reported in the literature. Further studies are needed to investigate the possible explanations, which might include decreasing sensitivity of tissue

to prednisolone, or progression in the severity of PLE.

Subcutaneous administration of heparin was also noted to have an effect in the relief of symptoms of PLE.[28,29] Heparin is a complex proteoglycan that resides in mast cells and throughout the body as a bound constituent of cell membranes and extracellular matrix proteins. It is also known as an integral component of the basement membrane in numerous organs of the body including the intestinal wall.[28] The mechanism by which heparin relieves enteric protein loss is unknown. It is possible that exogenous heparin, given its lipophilic nature and strong ionic charge, competes for matrix binding domains where native proteoglycans may be inadequate to prevent protein leakage.[28] We tried heparin therapy in two of our patients, but it showed only a transient effect.

In conclusion, PLE is a life-threatening complication after the Fontan operation. The most frequent symptoms are edema and effusion. Laboratory tests to confirm and evaluate PLE include serum albumin and total protein level, urinalysis, liver function test, fecal α-1-antitrypsin, echocardiography and electrocardiography. Immediate cardiac catheterization is required for complete hemodynamic evaluation. Surgery for residual hemodynamic lesions or creation of a surgical fenestration should be performed before cachexia develops. Current treatments for PLE, both medical and surgical, are associated with a very high mortality rate. Further investigation is needed to elucidate the exact mechanism of PLE and to find new therapeutic approaches.

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Fontan 式手術後蛋白質流失腸病變：九病例的臨床分析

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背 景： Fontan 式手術後常合併體靜脈血壓上升，腸淋巴系統壓力升高及腸道蛋白質流失。蛋白質流失腸病變是 Fontan 式手術後一個嚴重且可致死的併發症。本文目的在回顧本院病患蛋白質流失腸病變的發生率、臨床表現、診斷方法、治療方式及治療結果。

方 法： 分析自 1985 年 7 月至 2005 年 10 月，因爲複雜性先天性心臟病在本院接受各種不同形式的 Fontan 式手術病患的醫療記錄。蛋白質流失腸病變的診斷，是根據病患的臨床表現及實驗室的檢查結果而定。

結 果： 共有 101 位病患在此期間在本院接受不同形式的 Fontan 式手術，術後存活超過 30 天的 75 位病患中，有九位 (12%) 產生蛋白質流失腸病變，爲 4 男 5 女。其接受 Fontan 式手術的年齡中位數爲 6.3 歲 (3.3 - 12.3 歲)。接受 Fontan 式手術後至產生蛋白質流失腸病變的期間中位數爲 3.7 年 (1.2 - 9.7 年)；發病後追蹤期間中位數爲 4.9 年 (0.2 - 10.2 年)。9 位病患的臨床症狀爲：眼皮、臉部、陰囊或下肢水腫、腹水、腹瀉或呼吸困難。血中白蛋白 (albumin) 爲 2.0 ±0.6 mg/dL；總蛋白 (total protein) 爲 3.8 ±0.6 mg/dL。有 5 位病患檢測糞便中 α-1-antitrypsin 含量，都呈現升高。4 位接受小腸切片檢查，發現有淋巴管擴張 (lymphangiectasis) 及淋巴球浸潤增加。發病後有 6 例接受心導管檢查，其右心房壓力升高爲 22.5 ±5.8 mmHg。治療方式包含：高蛋白低脂肪飲食、白蛋白靜脈注射、利尿劑、強心劑、皮質類固醇 (corticosteroids)、肝素 (heparin) 以及外科手術。4 位病患只接受內科療法，其中 2 例分別因敗血症及心室功能衰竭死亡，其餘兩例仍須間歇注射白蛋白。另 5 位病患接受手術治療其蛋白質流失腸病變，其中 3 例因手術死亡，兩例術後蛋白質流失腸病變之症狀消失，但一例於術後 8 年後死於心室頻脈。共有 6 位病患死亡 (67%)。

結 論： Fontan 式手術後引起的蛋白質流失腸病變是一有生命危險的併發症。目前的內外科治療方式仍合併很高的死亡率。蛋白質流失腸病變的眞實致病機轉及新的治療方式仍有待進一步研究。

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關鍵字： 蛋白質流失腸病變，Fontan 式手術。

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