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심장질환에서 발생한 단백질 소실성 장염의 장기 경과에 대한 연구

Long term outcome of protein-losing enteropathy in cardiac disease

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ABSTRACT

Long term outcome of protein-losing enteropathy in cardiac disease

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Introduction: Protein-losing enteropathy (PLE) is a devastating complication of cardiac disease, especially after Fontan operation. The purpose of this study was to investigate the clinical characteristics, the responsiveness to the treatment options, and outcome of PLE patients at a single institution. Also we also tried to determine the successful treatment modality and the factors associated with the adverse outcome.

Methods: We reviewed medical records of 34 patients (12 female, 22 male) with PLE from cardiac disease from 1992 to 2016.

Results: Median age at PLE diagnosis was 11.4 years (range

0.8-28.3). The follow-up duration was 7.7±5.8 years. The underlying cardiac disease was functional single ventricle in 26 patients (76%), constrictive pericarditis in 3 patients (9%), valvular heart disease in 1 patient (3%), and restrictive cardiomyopathy in 1 patient (3%). Most patients (73%) underwent Fontan operation and 5 patients (14%) did not receive any surgery. PLE occurred in 4.5% of patients after Fontan operation. The survival rate was 80.7% at 5 years and 73.9% at 10 years. Twelve patients died during follow-up in 6.9±5.9 years after PLE onset. Aortic oxygen saturation<90% (HR=10.755 P=0.042), hemoglobin level<12g/dl (HR=6.520, P=0.023), decreased ventricular function (HR=5.094, P=0.024), NYHA functional class III or IV (HR 5.522, P=0.017) were predictors of mortality in PLE patients after Fontan operation. For the management of PLE, medical treatments were more frequently used including diuretics, ACEI/ARB, diet modification, subcutaneous heparin injection, oral corticosteroids. Interventional and surgical therapies such as Fontan pathway fenestration creation (4[16%]), Fontan conversion (4[16%]), and Fontan takedown surgery (2[8%]) were applied in selected

patients. One third of PLE patients after Fontan operation showed resolution of PLE. In Fontan patients, resolution of PLE was achieved by heparin in 4 patients, surgical Fontan fenestration in 2 patients, Aorto-pulmonary collaterals surgical ligation and transplantation in 1 patient each. Pulmonary vasodilator alone could not achieve resolution of PLE. Higher Fontan pathway pressure (16.8± 4.5mmHg vs. 13.0 ±1.9mmHg, P=0.02) was associated with intractable PLE.

Conclusions: The survival of PLE with cardiac disease has improved with the advancement of the conservative care. Although there is no definitive method, heparin and surgical/medical hemodynamic treatment led the resolution of PLE in one third of patient. Further investigation is also needed to determine the individual susceptibility of PLE as well as to develop new method of prevention and therapy.

Keywords: Protein-losing enteropathy, cardiac disease, Fontan operation, long-term outcome, survival rate, risk factor of mortality, intractablilily, resolution, treatment response

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LIST OF ABBREVIATIONS

PLE, Protein- losing enteropathy

BNP, B -type natriuretic peptide

NYHA, New-York Heart Association

AP, Atrio-pulmonary connection

LT, Lateral tunnel

ECC, Extra-cardiac conduit

DIRV, Double inlet right ventricle

DORV, Double outlet right ventricle

U-AVSD, Unbalanced atrio-ventricular septal defect

HLHS, Hypoplastic left heart syndrome

RCMP, Restrictive cardiomyopathy,

Stool AT, Stool alpha-antitrypsin

CRP, C-reactive protein

SVC, Superior vena cava

RA, Right atrium

EDP, End-diastolic pressure

AVVR, Atrio-ventricular valve regurgitation

EF, Ejection fraction

TPL, Transplantation

INTRODUCTION

Protein-losing enteropathy (PLE) is characterized by the abnormal loss of proteins such as albumin, immunoglobulin and clotting factor into gastrointestinal tract. The enteric loss of protein leads to peripheral edema, ascites, and diarrhea as well as malnutrition and growth failure. PLE can be caused by different disorders, with protein leakage through mucosal injury, as in inflammatory bowel disease and neoplasms or through lymphatic system abnormality as in primary intestinal lymphangiectasia and secondary intestinal lymphangiectasia including congestive heart failure, or after Fontan procedure. Cardiac diseases associated with PLE include constrictive pericarditis, restrictive cardiomyopathy, severe tricuspid insufficiency or stenosis and after Fontan operation. Especially, PLE has been reported in 5-15% of patients after Fontan operation and 50% mortality at 5 years after initial diagnosis. [1, 2] The most common factor in all of this cardiovascular disease is the elevated systemic venous pressure. Usually the patients who underwent Fontan operation had higher venous pressure

than normal individuals. But not all patients after Fontan operation manifest PLE. [1] Actually there must be other factor associated with developing PLE such as genetic disposition. [3] The exact mechanism of PLE complicated after cardiac diseases are poorly understood. Based on the various hypothesis about pathophysiology of PLE, numerous treatment have been used, including medical therapy[4] as well as interventional and surgical therapy.[5, 6] However only limited reports are available on the clinical characteristic, treatment response and outcome of the patients who have developed PLE associated with heart disease including Fontan patients. For the management of these potentially life threatening conditions, it is essential to scrutinize which approaches bring up to fail or success in PLE patients. Therefore we performed a retrospective cohort study of PLE patient associated with cardiac disease. The purpose of this study is to investigate the survival and resolution of patients with PLE who have had underline cardiovascular disease. Also we reviewed the hemodynamic, clinical characteristics and treatment strategies of patients with PLE related cardiac disease including after Fontan state. We sought to determine factor

associated with patient mortality and resolution and to review treatment strategies used in resolution patients.

METERIALS AND METHODS

1. Subject

We retrospectively reviewed a total of 37 patients (male in 23) who had developed PLE associated with cardiac disease between 1992 and 2016. For this study, the last follow-up ended at the July 2016. PLE was defined as the presence of hypoalbuminemia (serum albumin <3.5g/dl) accompanied by edema, ascites, diarrhea or pleural effusion, and presence of elevated stool alpha-1 antitrypsin concentration or clearance. The patients with renal protein loss had been excluded. The patients with mild chronic hepatic fibrosis with total bilirubin level < 3.0mg/dl with definitely increased stool alpha-1 antitrypsin concentration or clearance at the initial hypoalbuminemia. We excluded 3 patients who were lost to follow-up. Finally total 34 patients were enrolled in our cohort. Among 34 patients, 25 patients had diagnosed to PLE after the Fontan operation. Of the 25 patients identified, 21 patients (84%) had their original Fontan operation performed at the Seoul national university children's hospital, whereas 4(16%) had their original Fontan operation performed

elsewhere. PLE was developed in 4.5% of patients after Fontan operation which were performed from 1986-2016 in our institution. (22/487) Data were collected by retrospective chart review. Underlying cardiac disease, methods of the operation, treatment course, the response for treatment assessed by laboratory, hemodynamic data and outcome were investigated. For those who had undergone Fontan operation, the presence of initial Fontan pathway fenestration and the patency of Fontan fenestration at PLE diagnosis were reviewed. Echocardiographic data were reviewed for the presence of valvular regurgitation, ventricular systolic and diastolic function at the time of PLE diagnosis. The hemodynamic data were obtained from the cardiac catheterization within 2 years following diagnosis of PLE in most patients. For 2 patients, data were obtained from catheterization 5years following diagnosis of PLE. The data on the serum albumin levels, serum calcium levels, C-reactive protein, B type-natriuretic peptide and stool alpha-1 antitrypsin concentration at PLE diagnosis were obtained. Also concomitant presence of radiologic features of liver cirrhosis (RLC), anemia and arrhythmia were reviewed. RLC was diagnosed based on the

presence of irregular or nodular liver surface on ultrasonography or computed tomography. Anemia was defined below 12g/dl of hemoglobin at the time of PLE diagnosis. Clinically significant arrhythmia was defined as the need for arrhythmic drug therapy, pacemaker insertion or electrical cardioversion. Arrhythmia occurred after PLE diagnosis was excluded.

The two primary outcomes were a resolution of PLE and overall survival. We analyzed death, intractable state and response of each treatment for PLE patients in our hospital. For evaluation of response for treatment, we regarded following finding as the response to treatment; complete response was defined as serum albumin>3.5g/dl without albumin replacement for consecutive 3months, when the patient was consistently treated more than 4 months. Partial response was defined as serum albumin>3.0g/dl (3.0g/dl< albumin<=3.5g/dl) in the same manner. And we defined resolution of PLE as when the patient had none of following finding with or without maintaining mediation lasting 1years without relapse at least: (1) Hypoalbuminemia (<3.5g/dl) (2) Clinical manifestation such as edema and diarrhea (3) Elevated stool alpha-1 antitrypsin

concentration Because many PLE patients frequently developed recurrence. Intractable PLE was defined as when a patient had failed to maintain serum albumin levels over 3.5g/dl by any treatment at the present.

We analyzed the clinical characteristics, laboratory and hemodynamic features of PLE patient with cardiac disease. The patients were divided into two groups; 1) the survival and deceased, 2) the resolution and intractable status. Also we analyzed the prognostic factors for PLE patients after Fontan operation separately because Fontan state is special condition and shows poor prognosis itself. Variables used in the Cox regression analysis were initially analyzed as continuous variables, and then discrete cutoffs were selected based on the hazard ratios. The cutoffs were defined as follows: Aorta saturation at the time of PLE diagnosis (<90%), initial hemoglobin level (<12g/dl), ventricular end-diastolic pressure (>10mmHg), Fontan pathway pressure (<15mmHg). This study was approved by the Institutional Ethics Committee at the Seoul National University Hospital.

2. Statistical Analysis

All statistical analyses were conducted using the SPSS statistical package (version 19.0; SPSS, Chicago, IL). Continuous variables are expressed as mean ± SD or median (interquartile range) when appropriate. Variable Differences between groups were examined using the Mann-Whitney test, Fisher exact test where appropriate. Frequencies with proportions were determined for categorical variables. Survival analysis was performed by the Kaplan-Meier estimation, for the comparison of subgroup survival mantel-cox log rank analysis was performed. Due to the small sample size, Variables were examined through the univariate and multivariate Cox proportional hazards regression analysis. A P-value of <0.05 was considered statistically significant.

RESULTS

1. Patient demographics

A total of thirty-four patients with PLE from cardiac disease were identified. These included 25 patients who had undergone Fontan operation. The patient demographics are summarized in table 1. Median age at diagnosis of PLE was 11.4years (range 0.8-28.3). The follow-up duration was 7.7±5.8 years(range 0.2-18.8). Underlying cardiac diagnosis is summarized at table 1. Primary cardiac diagnosis was functional single ventricle which was required Fontan palliation in 26 patients (76%). Congenital heart disease with biventricle and acquired heart disease were in 8 patients (24%). Of them, constrictive pericarditis was in 3 patients (9%). Restrictive cardiomyopathy and Tricuspid regurgitation was in 1 patient (3%) each. (Figure 1A) In single ventricle patients, the predominant ventricle morphology was right ventricular in 17 patients (50%). The presenting clinical manifestation at initial diagnosis of PLE was edema (78%), diarrhea (8%), and dyspnea (3%). Four patients (11%) was diagnosed PLE due to incidental hypoalbuminemia.

Esophagogastroduodenoscopy was done in 15 patients and intestinal lymphangiectasia in duodenum was documented 10 patients (66%). (Figure 2)

At the time of diagnosis of PLE, the patients with NYHA classification I or II and III or IV were 26 and 8 patients (76% and 24%) respectively. RLC was founded in 18 patients (53%) of total patients and 17(68%) in Fontan patients at the time of PLE diagnosis. Anemia was found in 12 patients (35%) of total patients and 9(36%) in Fontan patients. At the time of PLE diagnosis, tachyarrhythmia including atrial flutter, fibrillation, atrial tachycardia, junctional ectopic tachycardia was in 10 patients (29%) of total patients and 9(36%) of Fontan patients. Two Fontan patients and one constrictive pericarditis patient developed atrial flutter and fibrillation early after PLE diagnosis. 2patients with biventricle repair and restrictive cardiomyopathy were experienced ventricular tachycardia after diagnosis of PLE. 9 patients (37%) of total patients and 6 (24%) of Fontan patients underwent pacemaker insertion due to sinus node dysfunction and complete atrio-ventricular block. Table2 demonstrated clinical characteristics in our study patients.

Table 1 Patient Demographics (N=34)

Male, N (%)	22(64)
Median age at PLE diagnosis (yrs)	11.4(0.8-28.3)
Median age at main operation (yrs)	3.1(0.4-26.4)
Median time : main operation[a] to PLE (yrs)	9.6(0.2-24.9)
Primary diagnosis, N (%)	
Functional single ventricle	26(76)
DIV	6(18)
DORV, hypo LV	6(18)
Unbalanced AVSD	4(12)
TA/TS	4(12)
MA/MS	1(3)
HLHS/variant	3(9)
Others	2(6)
Congenital or acquired heart disease with biventricle	8(24)
DORV with PS	3(9)
Restrictive cardiomyopathy	1(3)
Constrictive pericarditis	3(9)
Tricuspid regurgitation	1(3)

a**.** Including Fontan operation, biventricular repair surgery before diagnosis of PLE

Values are median (range) and N (%). Abbreviations: N, number; yrs, years; PLE, protein losing enteropathy; DIV, double inlet ventricle; DORV, double outlet right ventricle; hypo LV, hypoplastic left ventricle; AVSD; atrio-ventricular septal defect; TA/TS, tricuspid atresia/stenosis; MA/MS, mitral atresia/stenosis; HLHS, hypoplastic left heart syndrome; PS, pulmonary stenosis

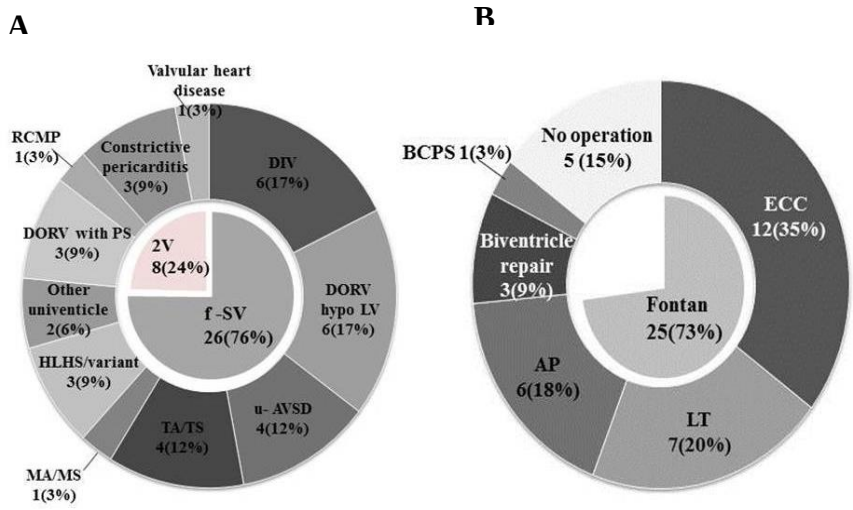


Figure 1 A. Primary heart diagnosis, B. Surgical history in study patients

Abbreviations: 2V, biventricle; f-SV, functional single ventricle; DIV, double inlet ventricle; DORV, double outlet right ventricle; hypo LV, hypoplastic left ventricle; u-AVSD; unbalanced atrio-ventricular septal defect; TA/TS, tricuspid atresia/stenosis; MA/MS, mitral atresia/stenosis; HLHS, hypoplastic left heart syndrome; PS, pulmonary stenosis; RCMP, restrictive cardiomyopathy; AP, atriopulmonary connection; LT, Lateral tunnel; ECC, extracardiac conduit; BCPS, bidirectional cavopulmonary shunt

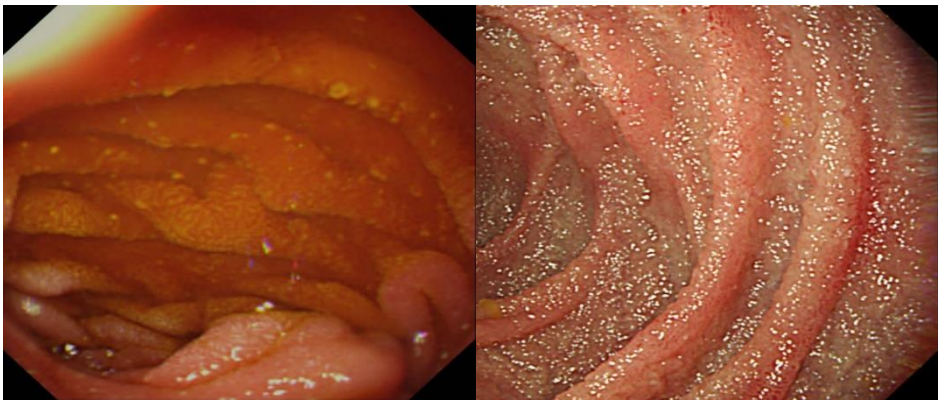


Figure 2
Intestinal lymphangiectasia in duodenum on esophagogastroduodenoscopy of PLE patients after Fontan operation

Table 2 Clinical characteristics at time of PLE diagnosis in Fontan patients/non-Fontan patients/Total patients

	Fontan (N=25)	Non-Fontan (N=9)	Total (N=34)
Ventricular morphology, N (%)			
Left ventricle	6(24)	0(0)	6(85)
Right ventricle	16(64)	1(11)	17(50)
Biventricle	3(12)	8(89)	11(32)
Heterotaxia syndrome, N (%)			
Left	1(4)	1(11)	2(6)
Right	5(20)	0(0)	5(15)
Fontan type, N (%)			
AP	6(24)		
LT	7(28)		
ECC	12(48)		
Presence of initial fenestration, N (%)	11(44)		
Presence of patent fenestration, N (%)	7(28)		
NYHA III or IV, N (%)	6(24)	2(29)	8(24)
Radiologic liver cirrhosis, N (%)	17(68)	1(11)	18(53)
Tachyarrhythmia, N (%)	12(48)	4(44)	16(47)
Pacemaker insertion, N (%)	6(24)	3(33)	9(37)
Anemia, N (%)	9(36)	3(33)	12(35)
Number of cardiac surgery before PLE	2.9±1.2	2.0±2.6	2.7±1.7

Abbreviations: N, number; AP, atriopulmonary connection; LT, Lateral tunnel; ECC, extracardiac conduit; NYHA, new York heart association; PLE, protein losing enteropathy

2. Surgical history

Of the total 34 patients, 25(73%) patients underwent Fontan operation. An atrio-pulmonary (AP) Fontan connection was performed in 6(17%); lateral tunnel (LT) Fontan was performed in 7(20%), extra-cardiac conduit (ECC) Fontan operation was performed in 12 (48%). In 25 Fontan patients, 12 patients (48%) has initial Fontan pathway fenestration and among them 7patient (28%) has patent Fontan pathway fenestration at initial PLE diagnosis. In 7 Fontan patients (28%), PLE was developed early after the further heart surgery; Fontan conversion operation in 2 and valve surgery in 5.

Three patients had biventricular repair and 1 patient was developed PLE at Bidirectional cavo-pulmonary shunt state under 1year old. (Figure1B)

Five patients had no surgery history before developing PLE which included 3 constrictive pericarditis, 1 restrictive cardiomyopathy and 1severe tricuspid regurgitation.

3. Hemodynamic and laboratory assessment

The mean total serum albumin level was 2.4±0.5 g/dl. Twenty nine patients had stool alpha 1-antitrypsin concentration which mean value was 351.6±298.5mg/dl. (Normal range: below 54mg/dl) The laboratory data and hemodynamic data are summarized in table 3. Superior vena cava pressure was 14.8± 4.3mmHg and right atrium pressure was 14.9±4.9mmHg. Fontan pathway pressure was mean 15.3±4.1 mmHg. Constrictive pericarditis and restrictive cardiomyopathy patients showed markedly elevated ventricular end diastolic pressure in 22mmHg and 21mmHg each. However there are no significant differences in hemodynamic data between Fontan group and non-Fontan group who had biventricular physiology except aorta oxygen saturation and pulmonary artery pressure. (p=0.033, p=0.010) Grade III, IV of atrio-ventricular valve regurgitation was present in 8 patients (24%) of total patients and 6patients (24%) of Fontan patients. Grade II of aortic valve regurgitation was existed in 4 patients (15%). 8 patients (24%) of total patients and 6 patients (24%) of Fontan patients had ventricular dysfunction at the time of PLE diagnosis.

Table 3 Laboratory and Hemodynamic assessment at the time of PLE diagnosis in Fontan patients/non-Fontan patients/Total patients

	Fontan (N=25)	Non-Fontan (N=9)	Total (N=34)
Albumin (g/dl)	2.3±0.5	2.6±0.36	2.4±0.5
Stool AT (mg/dl)	376.3±275.7	296.6±355.5	351.6±298.5
BNP (pg/ml)	192.9±541.6	670.4±954.5	312.3±681.2
Creatinine (mg/dl)	0.6±0.2	0.6±0.3	0.6±0.2
CRP (mg/dl)	0.7±1.0	0.9±1.6	0.7±1.1
Calcium (mg/dl)	8.1±0.7	8.3±0.9	8.1±0.7
Hemoglobin (g/dl)	12.9±3.1	12.7±2.4	12.9±2.7
SVC pressure (mmHg)	15.0±3.4	13.8±7.1	14.8±4.3
Fontan pathway pressure[a] (mmHg)	15.3±4.1	13.3±7.2	14.9±4.9
Mixed venous saturation (%)	64.6±7.9	64.9.±13.6	64.7±9.2
Ventricular EDP[b] (mmHg)	9.5±3.5	13.7±6.4	10.5±4.6
Pulmonary artery pressure[c] (mmHg)	14.1±3.4	18.4±1.8	14.9±3.5
Aorta oxygen saturation[c] (%)	92.3±3.5	91.9±14.4	92.2±7.1
Cardiac index (l/min/m^2)	2.9±0.7	3.3±1.3	3.0±0.8
PVR (WU)	1.7±0.6	7.6±9.9	2.7±4.2
AVVR Grade III-IV, N (%)	6(24)	2(22)	8(24)
AR Grade >II, N (%)	4(15)	1(11)	5(15)
Ventricular dysfunction, N (%)	6(24)	2(22)	8(24)

a: Right atrial pressure in biventricle patients

b: VEDP: dominant ventricle in functional single ventricle, Right ventricle in biventricle.

c: Pulmonary artery pressure and Aorta saturation showed significant difference between Fontan and non-Fontan group. (p=0.010, p=0.033)

Values are mean ± SD. Abbreviations: Stool AT, stool a-antitrypsin; BNP, B-type natriuretic peptide; CRP, c-reactive protein; SVC, superior vena cava; EDP, end diastolic pressure; PVR, pulmonary vascular resistance; AVVR, atrio-ventricular regurgitation; WU, wood unit; AR, aortic regurgitation

4. Patients survival and factor associated with mortality

Survival rate was 80.7% at 5years and 73.9% at 10years after diagnosis of PLE. In Fontan patients, survival rate was 86.5% at 5years and 77.9% at 10years after diagnosis of PLE. (Figure 4) There were 12 deaths. The mean age of death was 17.05±11.68 years of age (range 1.17-40.00). The mean time interval from the PLE diagnosis to death was 6.92±5.92 years (range 0.17-16.67). The patients expired due to sepsis in 4, respiratory complications in 3, heart failures in 2, fatal arrhythmias such as ventricular tachycardia and fibrillation in 2, and brain infarction in 1. Three patients death was associated with their reoperation. The era of surgery, before 1995 vs. after 1995, was not related with survival in our study.

Clinical characteristics, laboratory and hemodynamic data were compared between the patient group of alive and dead. (Table 4) The heart failure with New York Heart The more Patients who died seems to have New York Heart Association (NYHA) functional class III, IV at the time of PLE diagnosis and ventricular dysfunction were more frequently found in the fatal group with weak statistical significance. (p=0.059) Laboratory

assessment revealed that hemoglobin levels were significantly lower in patients in deceased group compared with survival group. (9.8±3.5 vs. 13.8±1.9, p=0.007). And patients who died showed lower aortic oxygen saturation at the time of PLE diagnosis compared with survival patients. (88.3±3.3 vs. 93.6±2.5, p=0.011). Also mixed venous saturation was lower in deceased group compared with survival group. (58.6±6.1 vs. 66.6±7.6, p=0.033)

Kaplan-Meier Survival curves for patients shown in Figure 4 according to the risk factors. Risk factors associated with mortality were NYHA functional class III or IV (p=0.008), decreased ventricular function (p= 0.013), lower aortic oxygen saturation (<90%) (p=0.012) and lower hemoglobin level (<12g/dl) (p=0.007) at the time of PLE diagnosis.

Overall grade of the diastolic filling pattern and atrio-ventricular valve regurgitation degree, initial serum albumin, Fontan pathway pressure, ventricular end-diastolic pressure, central venous pressure, pulmonary artery pressure, cardiac index, concomitant presence of liver cirrhosis and arrhythmia were not associated with survival.

Table 5 tabulated the results of the univariate Cox proportional hazard analyses of potential predictors for mortality in Fontan group. Aorta saturation<90% (HR=10.755 P=0.042), hemoglobin level<12g/dl (HR=6.520, P=0.023), decreased ventricular function (HR=5.094, P=0.024), NYHA functional class III or IV (HR 5.522, P=0.017) were predictors of mortality.

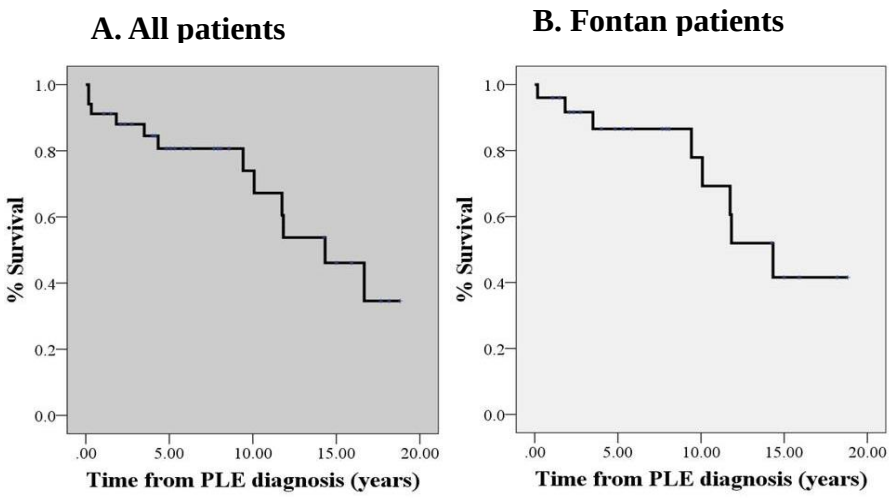


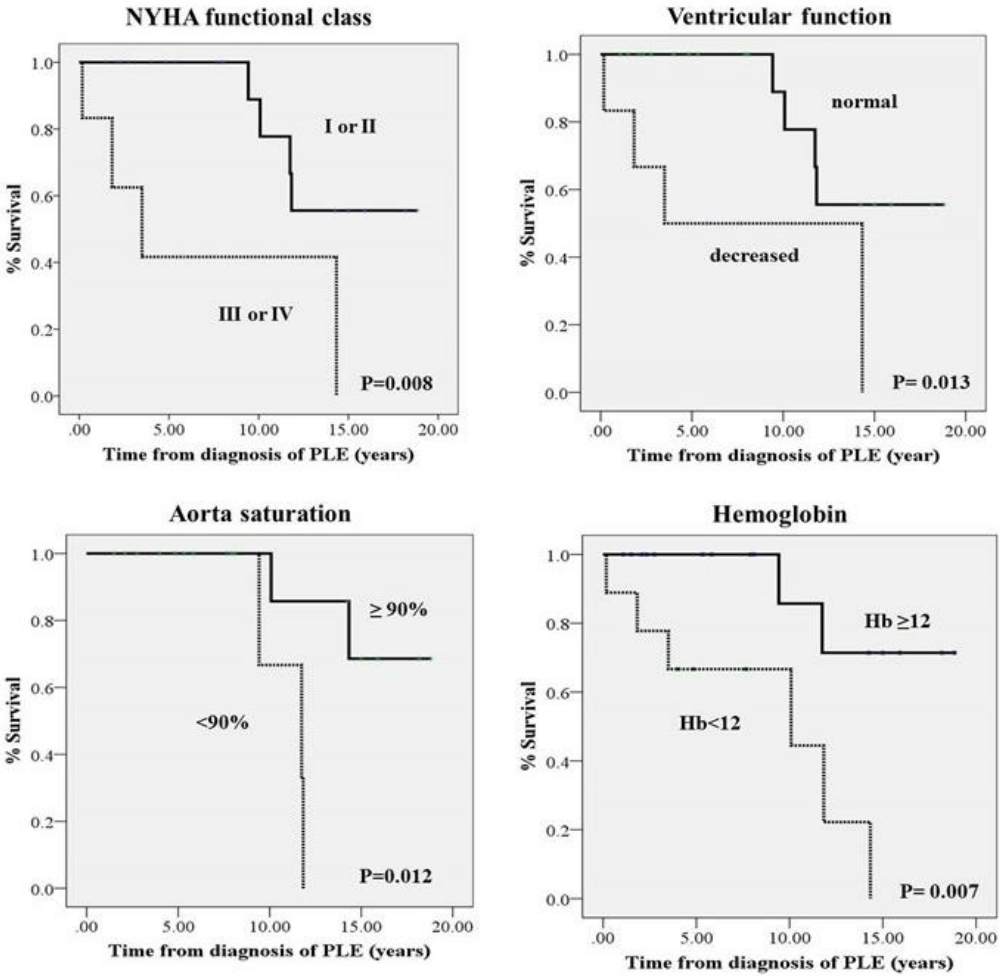
Figure 3 Overall survival rate of PLE with heart disease

Table 4 Clinical characteristics, Laboratory and Hemodynamic assessment at the time of PLE diagnosis between alive group and deceased group in Fontan

	Alive (N=17)	Deceased (N=8)	P-value
NYHA III-IV, N (%)	2(12)	4(50)	0.059
Radiologic liver cirrhosis, N (%)	7(41)	5(63)	NS
Tachyarrhythmia, N (%)	8(47)	4(50)	NS
Pacemaker insertion, N (%)	4(24)	2(25)	NS
Anemia, N (%)	3(18)	6(75)	0.01
Albumin (g/dl)	2.3±0.4	2.2±0.5	NS
Stool AT (mg/dl)	391.2±291.2	316.7±226.3	NS
BNP (pg/ml)	89.9±144.7	522.4±1100	NS
Creatinine (mg/dl)	0.5±0.1	0.6±0.2	NS
CRP (mg/dl)	0.6±0.7	0.8±1.4	NS
Calcium (mg/dl)	8.2±0.6	7.8±0.8	NS
Hemoglobin (g/dl)	13.8±1.9	9.8±3.5	0.007
SVC pressure (mmHg)	14.4±3.2	16.4±3.5	NS
Fontan pathway pressure (mmHg)	14.3±3.2	18.4±5.4	NS
Mixed venous saturation (%)	66.6±7.6	58.6±6.1	0.033
Ventricular EDP (mmHg)	9.7±3.9	9.0±2.9	NS
Pulmonary artery pressure (mmHg)	13.4±3.1	16.2±3.5	NS
Aorta oxygen saturation (%)	93.6±2.5	88.3±3.3	0.011
Cardiac index (l/min/m^2)	3.0±0.7	2.7±0.6	NS
PVR (WU)	1.8±0.6	1.5±0.4	NS
AVVR Grade III-IV, N (%)	4(16)	2(25)	NS
Ventricular dysfunction N (%)	2(12)	4(50)	0.059

Values are mean ± SD. Abbreviations: Stool AT, stool a-antitrypsin; BNP, B-type natriuretic peptide; CRP, c-reactive protein; SVC, superior vena cava; EDP, end diastolic pressure; PVR, pulmonary vascular resistance; AVVR, atrio-ventricular regurgitation; EF, ejection fraction

Figure 4. Kaplan-Meier plots showing the probability of survival when PLE patients were stratified by risk factor
: NYHA functional class Grade III or IV, ventricular function, Aorta oxygen saturation<90%, Hemoglobin <12 g/dL



Abbreviations: NYHA, New York Heart Association Classification; EF, ejection fraction; Hb, hemoglobin; PLE, protein losing enteropathy

Table 5 Univariate Cox Proportional Hazard analysis of predictors for mortality in Fontan patients

Variable	Hazard ratio (95% confidence interval)	P-value
Aorta oxygen saturation<90%	10.755(1.088-106.272)	0.042
Hemoglobin<12g/dl	6.520 (1.288-332.998)	0.023
Ventricular dysfunction	5.094(1.240-20.920)	0.024
NYHA III or IV	5.522(1.355-22.509)	0.017

Variables included in the univariate analysis that were not statistically associated with mortality were sex, age, ventricular morphology, operation type, initial serum albumin, stool alpha-1 antitrypsin, presence of liver cirrhosis, arrhythmia, other cardiac catheterization data such as Fontan pathway pressure, ventricular end diastolic pressure, cardiac index, mixed venous saturation, atrio-ventricular valve regurgitation.

5. Disease resolution and factors associated with intractability

Nine patients (36%) showed resolution longer more than 1year without recurrence in Fontan patients with PLE. 16 patients (64%) including 8 death were in uncontrolled disease state by multiple treatments ultimately. Of them, 9 patients (36%) experienced relapse of PLE even if they had partial or complete response for treatments. Serum albumin level and associated symptom had waxed and waned in many patients, especially the patients with medical treatment. In non-Fontan patients group, two patients of constrictive pericarditis showed long term complete resolution after surgical pericardiectomy. And one patient with tricuspid regurgitation and Noonan syndrome experienced complete response of PLE with steroid therapy. However 6 patients (67%) failed to increase serum albumin levels despite any treatment.

Table 6 summarizes clinical characteristics and laboratory and hemodynamic assessment at the time of PLE diagnosis of the two group in Fontan patients; resolution of PLE and intractable PLE. Higher Fontan pathway pressure (16.8±4.5mmHg vs. 13.0±

1.9mmHg, P=0.02) was associated with intractable PLE significantly. Other variables were not significant difference between two groups.

The results of the univariate Cox proportional hazard analyses of potential predictors for intractable PLE demonstrated absence of initial Fontan fenestration (HR=3.339, p=0.042), Fontan pathway pressure >15mmHg (HR=4.847, p=0.043), Ventricular end diastolic pressure > 10mmHg (HR=3.565, p=0.033), NYHA functional class III or IV (HR =3.055 P=0.048) at the time of diagnosis PLE were predictors of intractability in Fontan patients. (Table 7) however, there is no significant factor in multivariate analysis.

Table 6 Clinical characteristics, Laboratory and Hemodynamic assessment at the time of PLE diagnosis between resolution group and intractable group in Fontan

	Resolution (N=9)	Intractable (N=16)	P-value
NYHA III-IV, N (%)	1(11)	4(25)	NS
Radiologic Liver cirrhosis, N (%)	2(22)	10(63)	0.063
Tachyarrhythmia, N (%)	3(33)	9(56)	NS
Pacemaker insertion, N (%)	1(11)	5(31)	NS
Anemia, N (%)	2(22)	7(44)	NS
Albumin (g/dl)	2.1±0.5	2.4±0.4	NS
Stool AT (mg/dl)	393.7±250.4	362.1±306.1	NS
BNP (pg/ml)	92.9±193.9	254.4±675.4	NS
Creatinine (mg/dl)	0.6±0.2	0.6±0.2	NS
CRP (mg/dl)	0.6±0.7	0.7±1.1	NS
Calcium (mg/dl)	8.2±0.7	8.0±0.6	NS
Hemoglobin (g/dl)	13.6±1.8	11.9±3.5	NS
SVC pressure (mmHg)	13.5±2.2	15.9±3.6	NS
Fontan pathway pressure (mmHg)	13.0±1.9	16.8±4.5	0.02
Mixed venous saturation (%)	63.5±8.8	65.3±7.6	NS
Ventricular EDP (mmHg)	7.7±2.3	10.6±3.8	NS
Pulmonary artery pressure (mmHg)	12.7±2.4	15.0±3.7	NS
Aorta saturation (%)	92.8±2.1	91.9±4.2	NS
Cardiac index (l/min/m^2)	2.7±0.7	3.1±0.6	NS
PVR (WU)	1.9±0.7	1.6±0.5	NS
AVVR Grade III-IV, N (%)	3(30)	4(25)	NS
Ventricular dysfunction N (%)	1(11)	5(32)	NS

Values are mean ± SD. Abbreviations: Stool AT, stool a-antitrypsin; BNP, B-type natriuretic peptide; CRP, C - reactive protein; SVC, superior vena cava; EDP, end diastolic pressure; PVR, pulmonary vascular resistance; AVVR, atrio-ventricular regurgitation

Table 7 Univariate Cox Proportional Hazard analysis of predictors for intractability in Fontan patients

Variable	Hazard ratio (95% confidence interval)	P-value
Absence of initial Fontan fenestration	3.339(1.047-10.651)	0.042
Fontan pathway pressure>15mmHg	4.467(1.047-19.062)	0.043
Ventricular end diastolic pressure>10mmHg	3.565(1.111-11.442)	0.033
NYHA III or IV	3.055(1.010-9.245)	0.048

Variables included in the univariate analysis that were not statistically associated with mortality were sex, age, ventricular morphology, operation type, initial serum albumin, stool alpha-1 antitrypsin, presence of liver cirrhosis, arrhythmia, other cardiac catheterization data such as aorta oxygen saturation, mixed venous saturation, cardiac index, pulmonary vascular resistance , atrioventricular valve regurgitation.

6. Treatment and response in our experience

Medical theraphies were used in all patients with PLE. Twenty one patients(62%) received medical therapy only and 13 patients received medical plus surgical therapy. Type s of therapies were described in table 8.

Medical hemodynamic support such as diuretics and intravenous albumin replacement were used all patients. Especially, ARB/ACE inhibitor and digoxin were used in the majority of Fontan patients with PLE. Subcutaneous unfractionated heparin was used in 21 patients (62%) and steroid was used in 15 patients (47%). Pulmonary vasodilator such as sildenafil and beraprost was used in 13 patients (44%). 10 patients (29%) who had atrial arrhythmia took anti- arrhythmic drug such as sotalol or atenolol.

In the patients with specific hemodynamic abnormalities, the surgical and interventional therapies were also performed. In Fontan patients, Fontan fenestration, Fontan conversion, Fontan take-down, systemic-pulmonary collaterals ligation and heart transplantation were performed. One patient with biventricular repair and two patients of constrictive pericarditis underwent

surgical pericardiectomy.

Table 9 showed the response rate of each treatment in Fontan patients in our hospital. Total 5 patients brought resolution of PLE in medical therapy. All Fontan patients with PLE received hemodynamic support medical treatment including diuretics and iron deficiency anemia treatment, but 3 patients showed response and only 1 patient showed resolution by hemodynamic supportive medication alone. The heparin alone or heparin with pulmonary vasodilator was frequently used. Heparin use group showed resolution in 4 patients which is 21% of total heparin use group in Fontan patients. The more patients showed resolution in heparin use group compared with steroid or steroid combination group. Pulmonary vasodilator alone had not brought response and in case of combination with steroid or heparin, half patients showed response to therapy. The patients who had no response of heparin or steroid alone received steroid and heparin combination therapy. Steroid had 46% of therapy response rate, otherwise, albumin levels showed fluctuation depend on steroid dose and most patients experienced improvement and relapse of PLE, repeatedly

Selectively applied surgical therapies such as Fontan fenestration, Fontan takedown, and heart transplantation showed resolution more frequently. In our cohort, we had 3 patients who received late fenestration surgery and 1 patient who received early fenestration surgery. Of them, 2 patients showed resolution of PLE after late Fontan fenestration creation. 1 patient experienced PLE early after Fontan operation. In cardiac catheterization, Fontan pathway pressure revealed 12mmHg and Fontan fenestration brought response after 1 month. Otherwise another patient who had effect on fenestration diagnosed PLE in 3years after Fontan operation. Fontan pathway pressure revealed 12mmHg and fenestration was done in 2months after PLE diagnosis. However the patients showed response with hemodynamic supportive therapy in 13 months after fenestration. One patient who underwent late fenestration was expired due to pulmonary hemorrhage in 3month after surgery. And another patient who performed early fenestration after Fontan conversion was not effective despite high Fontan pathway pressure. (24mmHg)

Fontan conversion to extracardiac conduit was performed for

treatment of Fontan failure in 4 patients. However Fontan conversion was not effective for treatment of PLE in all patients. There is one patient who died after Fontan takedown and biventricular repair due post-operative heart failure. Recently, one patient underwent delayed Fontan take-down for the purpose of treatment of PLE and severe hepatic dysfunction. This patient showed partial response with steroid and pulmonary vasodilator after Fontan takedown. One patient who received ligation of Aorto-pulmonary collaterals was in resolution.

The one Fontan patient who showed response in steroid and pulmonary vasodilator combination therapy was in long term resolution after heart transplantation.

In non- Fontan patients, one patient experienced complete response after hemodynamic supportive care only but PLE was relapsed. Two constrictive pericarditis patients who received surgical pericardiectomy showed resolved PLE. However one patient who diagnosed Fallot type DORV with AVSD biventricular repair was still suffered from intractable PLE in spite of pericardiectomy and heart transplantation.

Table 10 summarized the 9 cases who achieved resolution of

PLE. In those patients, the definitive modality was applied in 17.4 ±29.7 month after PLE diagnosis. PLE showed response in 6.8 ±6.3month after application of effective treatment and finally they remained in resolution state for in 6.24±5.3 years.

Table 8 Type of treatment in all patients

N (%)	Alive (N=17)	Death (N=8)	Total (N=25)	(N=9)	(N=34)
Fontan			**Fontan**	**Non-Fontan**	**All**
Medical therapy					
Diuretics	17(100)	8(100)	25(100)	9(100)	34(100)
Digoxin	14(82)	7(87)	21(84)	3(33)	24(71)
Warfarin	13(77)	7(88)	20(80)	4(44)	24(71)
ACEI/ARB	16(94)	8(100)	24(96)	5(56)	29(85)
Low fat + MCT oil	12(71)	5(63)	17(68)	6(67)	23(68)
Heparin	13(76)	6(75)	19(76)	2(22)	21(62)
Iron+transfusion	7(41)	7(88)	14(56)	4(44)	18(53)
Steroid*	8(47)	5(63)	13(52)	2(22)	15(47)
Pulmonary vasodilator [a]	8(47)	2(25)	10(40)	3(33)	13(44)
IVIG	7(41)	5(63)	12(48)	4(44)	16(46)
Antiarrhythmic drug	5(29)	3(38)	8(32)	2(22)	10(29)
Octreotide	0(0)	0(0)	0(0)	1(11)	1(3)
Surgical therapy					
Fontan fenestration	4(24)	1(13)	5(20)	-	-
Fontan conversion	1(6)	3(38)	4(16)	-	-
Fontan take down	1(6)	1(13)	2(8)	-	-
Heart transplantation	1(6)	0(0)	1(4)	1(11)	2(6)
Collateral ligation	1(6)	0(0)	1(6)	0(0)	1(3)
Pericardiectomy	3(13)	0(0)	0(0)	3(33)	3(9)

a. included sildenafil, beraprost, bosentan, and ventavis;

b. we analysis treatment of alive and death in only Fontan patients

Abbreviations: ACEI, angiotensin converter enzyme inhibitor; ARB, angiotensin receptor blocker; MCT, medium chain triglyceride; IVIG, intravenous immunoglobulin

Table 9 Response rate of each treatment for PLE in Fontan patients

Treatment	Use[a]	No response[b]	Response rate[b]	Resolution rate[b]
Medical	**N(%)**	**N(%)**	**N(%)**	**N(%)**
Hemodynamic support alone	25(100)	22(88)	3(12)	1(4)
Heparin[c]	19(76)	13(68)	6(32)	4(21)
Steroid[d]	11(44)	6(54)	5(46)	
Heparin+Steroid[e]	7(28)	5(71)	2(29)	
Pulmonary vasodilator alone	3(12)	3(12)		
***Pulmonary vasodilator + Heparin or Steroid[f]**	8(32)	4(50)	4(50)	1(13)
Surgical and interventional				
Fontan fenestration	5(19)	3(60)	2(40)	2(40)
Fontan conversion	4(15)	4(100)		
Fontan takedown	2(8)		1(50)	
Heart transplantation	1(4)		1(100)	1(100)
Collateral ligation	1(4)		1(100)	1(100)

a. N/Total Fontan patients with PLE (25) (%), b. N/The number of patients who received that treatment (%)
c. Included heparin alone or with pulmonary vasodilator, d. Included heparin alone or with pulmonary vasodilator
e. In case that no response shows heparin alone or steroid alone
f. These patients were included heparin and steroid group above. We indicated this data separately to show that effectiveness of pulmonary vasodilator combination therapy.
All treatment was used with hemodynamic support. each treatment was used sequnetially in most cases. Response rate included parial and complete response

Table 10 Summary of resolution in PLE patient after Fontan operation

Patient	Fontan type (pre-dominant ventricle)	Sex/Age	Treatment for resolution	Time interval from therapy to response(month)	Time interval from diagnosis to therapy(month)	Relapse free-resolution time(year)
1	ECC(RV)	F/18yr	Supportive	1	0	2.1
2	LT (LV)	M/25yr	Heparin SQ	6	84	10.7
3	LT(RV)	F/28yr	Heparin SQ	8	0	3.3
4	ECC(RV)	F/8yr	Heparin SQ+Pulmonary vasodilator	2	23	2.8
5	ECC(RV)	M/18yr	Heparin SQ	17	0	2.6
6	ECC(RV)	M/15yr	Steroid+Pulmonary vasodilator, TPL	0.5	47	2.3
7	ECC(RV)	M/10yr	Fontan fenestration	1	1	7.9
8	ECC(LV)	M/14yr	Fontan fenestration	15	0	6.7
9	LT(RV)	M/23yr	collateral artery ligation	11	2	17.8

Abbreviations: ECC, extracardiac conduit; LT, lateral tunnel; LV, left ventricle; RV, right ventricle; SQ, subcutaneous injection; TPL,transplantation

DISCUSSION

We present the long-term follow-up study from a single institution for patients who were diagnosed with PLE associated with cardiac disease. Historically, the survival rate of PLE patients was about 50% at 5 years after diagnosis in 1985. [7] However survival rate in PLE from cardiac disease was 80.7% at 5 years and 73.9% at 10 years in our cohort. Also, a recent single-center study by John and colleagues has reported improved survival rate in PLE patients after the Fontan procedure. [8] This has been partially attributed to better surgical techniques and an improvement in postoperative management after the Fontan operation. [9] However, the timing of surgery was not associated with survival in our study because half of the mortalities occurred in patients who underwent an initial Fontan operation after 1995. Therefore, earlier diagnosis of PLE may have contributed to an improvement in survival. In addition, it may be due to the comprehensive assessment into the causes of the PLE and the versatile aggressive treatment. Nevertheless, there is still a high mortality rate in PLE patients

associated with cardiac disease and it continues to remain difficult to control PLE. In our cohort, 65% of total patients with PLE had no improvement despite treatment and half of them finally died.

PLE with cardiac disease is mostly associated with chronically elevated systemic venous pressure.[2] In some cases, PLE can be resolved through decreasing systemic venous pressure such as surgical pericardiectomy for constrictive pericarditis.[10] Constrictive pericarditis results in the elevation of central venous pressure, congestion of bowel wall lymphatic vessels and direct leakage via the surface epithelium of plasma proteins. It is also typically presented with the manifestation of lower cardiac output because deteriorated left ventricle filling is related to a decrease in stroke volume. [10] In our cohort, we found that the symptoms of PLE were alleviated in two patients with constrictive pericarditis by surgical pericardiectomy. However, pericardiectomy was not effective in one patient with AVSD and pulmonary stenosis who underwent biventricular repair and secondary constrictive pericarditis. The surgical pericardiectomy was inadequate due to massive adhesion and

calcification of pericardium which resulted from several heart operations. In addition, because multi-organs were already damaged and irreversible bowel change had progressed, this patient still suffered intractable PLE despite a heart transplantation.

The precise pathophysiology of PLE after the Fontan operation is poorly understood. To the best of our knowledge, higher systemic venous pressure and low cardiac output status may be related to altered mesenteric circulation developing into PLE after the Fontan operation.[11] In response to chronic low cardiac output, the patients exist in a relatively inflamed state, with an increased level of tumor necrosis factor (TNF) alpha.[12] It leads to diminished intestinal perfusion, which may contribute to a break in the intestinal integrity and protein leak.[3] However, although relatively elevated systemic venous pressures in comparison with the normal heart are avoidable, not all Fontan patients manifest PLE. Also, a high systemic venous pressure in cardiac catheterization does not always provoke PLE. In actual fact, there must be other factors associated with developing PLE.

We identified factors associated with mortality on the basis of

clinical characteristics and laboratory and hemodynamic data at the initial diagnosis of PLE. The patients who died had a decreased cardiac index compared with survivors (2.7±0.6 l/min/m^2 vs. 3.0±0.7 l/min/m^2, respectively). A high grade of NYHA functional classification (Gr III or IV), low hemoglobin level (<12g/dl), lower aorta oxygen saturation (<90%), and decreased ventricle function at the time of PLE diagnosis was associated with a significant mortality in patients with PLE after the Fontan operation. Similar to previous reports, our findings show that low cardiac output can influence survival in patients with PLE.

In Fontan patients, anemia, especially iron deficiency anemia is not uncommon and may be related in part to gastrointestinal blood loss in the face of portal hypertension from congestion as well as activation of pro-inflammatory cytokines such as TNF-alpha and its inhibition of erythropoietin.[13] Anemia is also well recognized as a marker of poor prognosis in patients with heart failure and is associated with lower cardiac functional status.[14, 15] In addition, anemia contributes to the development or propagation of PLE itself. The patients who died had low aorta

oxygen saturation and mixed venous saturation compared with patients who survived (88.3±3.3% vs. 93.6±2.5, 58.6±6.1 vs. 66.6±7.6 mmHg, respectively). Low aorta oxygen saturation was related to tissue hypoxia and mortality. Ventricular dysfunction represents the cause of decreased cardiac output. And the high grade of NYHA functional class reflects reduced cardiac functional capacity.

PLE after Fontan operation still remains poorly understood and has a miserable prognosis in comparison to other heart diseases related to PLE. Poor prognosis of patients with PLE can occur at markedly abnormal hemodynamics at the time of PLE diagnosis. We tried to identify potential predictors for intractability at the time of PLE diagnosis. High Fontan pathway pressure (>15 mmHg), elevated ventricular end diastolic pressure (>10 mmHg), the absence of initial Fontan fenestration and high-grade NYHA functional class III or IV were associated with predictive factor for uncontrolled PLE. High Fontan pathway pressure is related to elevated central venous pressure and leads to congestion and low cardiac output. This status can be trapped in a vicious cycle and more aggravated PLE disease activity. Elevated ventricular

end-diastolic pressure represents ventricular diastolic dysfunction. It is an important measure of ventricular performance and may identify patients at increased risk for developing late clinical symptoms of heart failure. The patients who had no initial Fontan fenestration had more intractable PLE compared with the patients who had. Creation of a systemic to pulmonary venous atrial level communication of fenestration at the time of Fontan completion may benefit patients by decompression of Fontan pathway pressure and creating a right to left shunt which may augment cardiac output and limit central venous pressure in the immediate postoperative period. [16] It can be helpful for improving postoperative hemodynamic stabilization.

As a result, we believe that patients with PLE who display these high-risk characteristics of mortality and morbidity should be evaluated comprehensively and managed more aggressively with multiple treatment modalities. Selected high-risk patients with PLE were considered for transplantation if the clinical situation was not improved.

In treatment of PLE with cardiac disease, correction of possible

underlying cause is most important. An exhaustive hemodynamic and laboratory assessment at initial diagnosis is essential. First, all patients with PLE are mandatory to hemodynamic evaluation through testing including cardiac catheterization and echocardiography. In case chronically elevated systemic venous pressure is present, such as constrictive pericarditis or venous obstruction, surgical and interventional correction, such as pericardiectomy, surgical relief of baffle obstruction are helpful.[17] The factors associated with low cardiac output, including atrioventricular valve regurgitation, residual coarctation of the aorta, multiple collaterals and arrhythmia which results in atrioventricular dysynchrony, should be considered for immediate correction especially in Fontan patients. Because the cause of PLE is multifactorial and unclear, it is important to individualize the treatment plan for each patient. [18]

Two treatment approaches are recommended to improve circulation and inhibit inflammation. As an initial treatment, most patients received medical treatment which aimed at symptomatic relief such as diuretics and intermittent infusion of intravenous albumin to improve hemodynamic status. A high protein and low-

fat diet supplemented with medium-chain triglyceride oil was introduced to most patients in our study. However, these modalities were associated with only transient relief of clinical symptoms and limited success in our patients. In the next step, intestinal therapy including subcutaneous unfractionated heparin or corticosteroid can be considered. Subcutaneous unfractionated heparin acts as a mechanical barrier by decreasing permeability of the basal membrane to large molecules such as albumin. [3] In our study, 76% of Fontan patients received heparin therapy, whether or not it is combined with other therapy, and 32% of patients showed a response. Twenty-one percent of heparin used patients experienced resolution by continuing the use of heparin. However, the initial response of heparin did not affect survival rate or resolution rate significantly. In a study by Ryerson and colleagues in 2008, 76% of their cohort patients who received heparin treatment experienced subjective symptomatic improvement and only 18% of patients went into clinical resolution. [19] In our patients, positive response and stable resolution were more likely to be achieved in heparin therapy than with corticosteroid or

pulmonary vasodilator therapy.

Corticosteroid has been used in patients with PLE associated inflammatory bowel disease or collagen vascular disease as well as after the Fontan procedure. Steroid has an anti-inflammatory effect and stabilizes the intestinal capillary or lymphatic membrane and decreases the intestinal lacteal dilatation, membrane permeability, and infiltration of leukocytes. Oral budesonide enteral targeted corticosteroid is a potentially attractive treatment option with relatively minimal systemic side-effects.[20] In our cohort, 44% of PLE patients with Fontan procedure experienced steroid therapy and half of them showed a response but none went into long term resolution because albumin level waxed and waned depending on steroid dose. Furthermore, complications due to steroid use such as infection, growth failure, and gastric ulcer were a more significant problem for maintaining steroid use.

Pulmonary vasodilators, such as sildenafil, beraprost, and bosentan, can be considered in the treatment option of PLE. This therapy effects a reduction of pulmonary vascular resistance and dilation of mesenteric vessels. Finally, it results in increased

mesenteric arterial flow and cardiac output. In our study, no patient experienced a benefit with pulmonary vasodilator alone. The combination therapy with pulmonary vasodilator and heparin or pulmonary vasodilator and steroid brought an improvement of PLE in some patients.

Surgical and interventional treatments brought a more dramatic resolution of PLE in selected patients including the creation of Fontan fenestration and aortopulmonary collateral vessel ligation. These operations can provide effective stabilization of failing Fontan patients including PLE, liver dysfunction and pump failure by decreasing venous pressure and increasing cardiac output. However surgical intervention should be undertaken only when the patient's clinical status has been optimized by all other means and when the potential hemodynamic benefit will be dramatic because the surgical mortality rates reported for patients with PLE are very high. For those patients with elevated systemic venous pressure, Fontan fenestration can theoretically improve cardiac output and decompress the Fontan pathway pressure to relieve PLE, although at the expense of hypoxemia and increased stroke risk. Early fenestration can be helpful to

failing Fontan such as pump failure early after the Fontan operation. In a report by Rychik and colleagues, of the five patients with PLE who had a late surgical fenestration, three had normalization of serum proteins and resolution of symptoms at 2 to 6 weeks. All three patients with PLE have remained asymptomatic with patency of the fenestration for 2 years. [17] However according to a report from Vyas and colleagues, a total of 16 PLE patients with fenestration creation through intervention resulted in no lasting resolution of PLE because of the technical difficulty in maintaining the patency of created fenestration in many patients. [21] Thus, creation of a durable fenestration is required to achieve sustained resolution of PLE in some patients. In experience with fenestration for PLE treatment at our institution, three patients received late surgical fenestration and of them, two patients resulted in the resolution of PLE. Interestingly, there was no recurrence after spontaneous fenestration closure in both patients.

Fontan conversion to an extra-cardiac circuit with anti-arrhythmic surgery is quite successful in patients with atrial tachyarrhythmia who underwent atriopulmonary type Fontan

connection because these connections often develop significant enlargement of the right atrium and less efficient flow dynamics. However, similar to a previous study, four patients with PLE who received Fontan conversion did not have improved PLE and of them, two patients had surgery related mortality. PLE seems to derive limited benefit from Fontan conversion, and the reported operative mortality rate approaches 50%. [2]

Another surgical solution for failing Fontan is Fontan pathway takedown. Fontan takedown has primary been used as a bailout option in early Fontan failure. In our institution, two of the patients received delayed Fontan takedown. One patient died due to persistent ventricular dysfunction after Fontan takedown and sequentially Rastelli operation. Delayed Fontan takedown procedure was performed in another patient who had liver dysfunction and PLE. It resulted in temporary improvement of albumin level from Fontan takedown. Thus, steroid and pulmonary vasodilator therapy were added and the patient is currently under close observation in the outpatient clinic. In a recent report written by Brizard and colleagues, a novel combined surgical and percutaneous approach for the treatment

of PLE in which they isolate the entire hepatic venous flow from the systemic blood flow in the Fontan circuit was successful mid-term treatment for PLE in two patients. [22]

Interestingly, we have one patient in resolution of PLE after aortopulmonary collateral vessel ligation. Significant aortopulmonary collateral vessels are identified as the source of a considerable left to right shunt and absorbed a sizable portion of the cardiac output. [23] It has the potential to cause an important flow energy dissipation which effects in patients with Fontan-type circulation. Therefore, systemic pulmonary collaterals occlusion has an effect of improving pulmonary perfusion and long-term cardiac performance. In a previous report, late postoperative chylothorax or pleural effusion was resolved after aortopulmonary collateral embolization. [24, 25] However there is no report about resolution of PLE after collateral ligation.

It is also notable that cardiac transplantation has been reported as a potential treatment strategy for failing Fontan. After cardiac transplantation, the patients experience an immediate response, sometimes the PLE could take time to improve and the patient

could need additional treatment such as short course of steroids.[26] Patients with PLE are high mortality and morbidity transplantation recipients. An elevated antibody titer, increased risk for infection, anatomical challenges and concomitant liver dysfunction combine to create a significant risk of mortality both in the period of waiting for a donor organ and immediate post transplantation. However, Schumacher and colleagues reported from the pediatric heart transplant study group that PLE was not associated with an increased risk of waitlist mortality or post-heart transplantation morbidity and mortality.[27] In our study, two patients underwent heart transplantation and one patient was in a resolved state of PLE early after post transplantation. However, another patient who had biventricular repair surgery showed poor outcome of intractable infection and bleeding in early post transplantation. Multiple reports have suggested successful heart transplantation could eliminate PLE. [28] Ultimately, it seems that a better condition of patient selection and earlier referral for consideration of transplantation may be essential for the improvement of outcome.

In the non-Fontan patient group, only two patients with

constrictive pericarditis were in resolution after surgical pericardiectomy and one patient with Noonan syndrome who had tricuspid regurgitation experienced complete response to steroid. This patient recently received cyclosporine therapy for newly developed membranous-proliferative glomerulonephritis.

In our cohort, 67% of total patients were intractable despite any treatment. In the Fontan group, 64% of patients showed no resolution of PLE despite multiple treatment modalities. More to the point, present resolution of PLE is not permanent, meaning not a "cure" for PLE. Maintenance of the resolution state is also important.

This study has several limitations. First, it may be that our sample size could have been too small to detect the influence of variables. Thus, there is a limitation in the multivariate Cox proportional hazard analysis. Second, some information given this retrospective study was not universally available. Because this study has an incompleteness of data, it is difficult for us to make a conclusion. Third, in our cohort, not all patients were initially diagnosed with PLE and underwent an initial operation at our center. Thus, center differences in patient evaluation and

first treatment choice could be present. Also, cardiac catheterization was not performed on all PLE patients at initial diagnosis. Ventricular function and valve regurgitation at diagnosis was obtained through data from echocardiography which was performed by a different person.

CONCLUSION

PLE after cardiac disease still remains difficult to treat, though survival has improved with the advancement in various treatments. It would be useful that those factors associated with mortality and morbidity in PLE are identified. Poor cardiac functional status, poor ventricular function, and anemia indicated that low cardiac output is associated with mortality. In addition, low aorta oxygen saturation indicated by decreased systemic oxygen perfusion also reduced survival. The presence of high-risk characteristics should prompt evaluations and consider a more aggressive management. In the treatment of PLE with cardiac disease, correction of possible causal factors related to elevated venous congestion, low cardiac output and increased

mesenteric vascular impedance is the first approach. In fact, in PLE after the Fontan operation, little is understood about why this ailment occurs and there is no clear-cut effective treatment. However, through perseverance investigation and trying drastic novel treatments, there are some reports about the resolution of PLE. According to the experience at our institution, resolution therapy was diverse and tailored to match individuals after comprehensive hemodynamic assessment. It is impressive and inspiring that nine patients (36%) who had PLE with Fontan were in resolution although an explanation of the exact mechanisms is limited. Further investigation is needed to determine the exact mechanism of PLE after heart disease and to develop new therapeutic approaches for improving patient outcomes, and we should share the experience of improving patient outcome.

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국 문 초 록

서론: 단백질 소실성 장염은 심장질환, 특히 폰탄 수술과 관련하여 발생하는 예후가 나쁜 합병증 중 하나이다. 본 연구의 목적은 심장질환과 연관되어 발생하는 단백질 소실성 장염의 임상적 특징과 치료, 그에 대한 반응 및 예후에 대해 알아보고자 한다. 또한 질병의 불량한 예후와 관련된 요인들에 대해 분석하고 본원에서 성공적으로 단백질 소실성 장염을 치료한 사례에 대해 알아보고자 한다.

방법: 1992년부터 2016년까지 서울대학교 어린이병원에서 진단 및 치료를 받았던 34명의 심장질환과 연관된 단백질 소실성 장염 환자를 대상으로 후향적 의무기록 조사를 통해 연구를 진행하였다.

결과: 단백질 소실성 장염을 진단받은 나이의 중간 값은 11.4세이었고 진단에서부터 마지막 외래 경과관찰까지의 시간은 평균 7.7년이었다. 기저 심장 질환으로는 26명의 환자가 기능성 단심실이었고 3명은 수축성 심막염이었으며 판막질환, 제한성 심장 근육병이 각각 1명이었다. 대부분의 환자들은 폰탄 수

술을 받은 환자였고 5명의 환자들은 심장 수술을 받은 병력이 없었다. 본원에서는 단백질 소실성 장염은 폰탄 환자의 4.5%에서 발병하였다. 누적 생존율은 5년에 80.7%, 10년에 73.9%였고 12명의 환자가 평균 6.9년 추적 관찰 중에 사망하였다. 대동맥 산소포화도 <90%, (HR=10.755, P=0.042), 헤모글로빈 <12g/dl (HR=6.520, P=0.023), 심실 수축력의 감소 (HR=5.094, P=0.024), NYHA 기능성 단계 정도 3-4 (HR=5.522, P=0.017)은 사망률을 예측할 수 있는 인자로 의미가 있었다. 대부분의 환자들은 내과적 치료를 받았고 이뇨제, 안지오텐신 수용체 길항제 / 안지오텐신 전환효소 억제제, 식이요법, 헤파린 피하주사 요법, 스테로이드제가 포함되었다. 이외에도 특정환자들은 폰탄 개창술(4[16%]), 폰탄 전환술 (4[16%]), 폰탄 전 단계로 돌아가는 수술(2[8%])을 포함한 중재적 또는 수술적 치료를 시행 받았다. 폰탄 이후에 발생한 단백질 소실성 장염 환자의 1/3이 여러 가지 치료를 통해서 호전을 보였다. 폰탄 환자에서는 4명의 환자가 헤파린 치료로 단백질 소실성 장염이 호전되었고, 폰탄 개창술로 2명, 대동맥 폐동맥 간 부행 동맥 결찰술, 심장 이식으로 각각 1명의 환자가 단백질 소실성 장염이

관해를 보였다. 하지만 폐혈관 확장제 단독으로는 단백질 소실성 장염의 관해가 오지 않았다. 높은 폰탄길 압력은 질병의 난치성 경과와 관련 있는 인자로 분석되었다. (16.8±4.5mmHg vs. 13.0±1.9mmHg, P=0.02)

결론: 다양한 치료방법의 발달로 인해 심장질환에서의 단백질 소실성 장염의 생존율은 향상되었다. 비록 확실한 치료방법은 아직 없으나 본 연구에서는 1/3의 환자들이 헤파린 또는 수술적, 약물적 혈역학적 치료들을 통해서 단백질 소실성 장염의 장기적 호전을 보였다. 단백질 소실성 장염의 예방과 새로운 치료 방법의 개발뿐 아니라 개개인의 단백질 소실성 장염에 대한 감수성을 규명하기 위해 보다 많은 연구와 노력이 필요할 것이다.

주요어: 단백질 소실성 장염, 심장 질환, 폰탄 수술, 장기적 예후, 생존율, 사망과 난치성과 관련된 위험요소, 관해, 치료방법과 효과

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