PROTEIN-LOSING ENTEROPATHY AFTER THE FONTAN OPERATION

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Patients were observed after the Fontan operation to determine the frequency and severity of protein-losing enteropathy. A total of 427 patients who survived for 30 days after the Fontan operation, performed between 1973 and January 1987, were analyzed and, thus far, protein-losing enteropathy has developed in 47 of 427. The cumulative risk for the development of protein-losing enteropathy by 10 years was 13.4% among 30-day survivors, and 5-year survival after the diagnosis was 46%. Hemodynamic studies done coincident with the diagnosis of protein-losing enteropathy have shown increased systemic venous pressure, decreased cardiac index, increased pulmonary vascular resistance, and increased ventricular end-diastolic pressure. Medical management of protein-losing enteropathy was only partially successful. Statistical analysis has shown that factors related to protein-losing enteropathy were ventricular anatomy, increased preoperative ventricular end-diastolic pressure, longer operative bypass time, increased length of hospital stay, and postoperative renal failure. This study suggests that scrupulous selection of cases for the Fontan operation is mandatory and that certain perioperative factors may predispose to this serious complication of the Fontan procedure. (*J Thorac Cardiovasc Surg* 1996;112:672-80)

Protein-losing enteropathy (PLE) associated with cardiovascular disease was first noted in patients in whom constrictive pericarditis developed¹ or those who had long-standing congestive heart failure.² PLE also has been reported in patients who have had the Mustard procedure for complete transposition of the great arteries and in whom obstruction of the intraatrial baffle had developed.³ It has been theorized that PLE results from increased systemic venous pressure that subsequently causes lymphangiectasis, which has been documented by jejunal biopsy. PLE associated with the Fontan operation was reported in 1980 and again in 1984.^{4, 5} A preliminary review of the experience at the Mayo Clinic was reported and the frequency of PLE after the Fontan operation was approximately 10%. For

another recent series⁶ a 24% frequency of PLE was reported after the Fontan operation.

The purpose of this study was to estimate the probability of PLE developing among 30-day survivors of the Fontan operation. In addition, the clinical course of patients with PLE was analyzed to determine survivability and to describe the effects of different options for management. Various preoperative and perioperative risk factors for the development of PLE were also assessed. An understanding of the occurrence and severity of this important complication of the Fontan operation, as well as a knowledge of certain risk factors that may be associated with PLE, can enhance the ability to select optimal candidates for the Fontan operation.

Methods

This report is based on patients who had the Fontan operation between 1973 and January 1987 at the Mayo Clinic and who were alive 30 days after the operation. A database for these patients has been used for previous publications.⁷⁻¹⁰ This database was updated by data from recent return visits, reports from local physicians, and information obtained from recent written questionnaires or telephone interviews. Recent follow-up information was available for all 30-day survivors except for five patients who were known to be alive 3 to 5 years after their Fontan operation. Excluded were patients whose Fontan repair was taken down in the first 30 days after the operation.

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Fig. 1. Survival curve for 427 30-day survivors of the Fontan operation. Time zero is 30 days after the operation.

Current data included vital status, cardiovascular symptoms or signs, medications and other management regimens, date of onset of PLE if present, clinical course, and results of pertinent echocardiographic or hemodynamic studies. PLE was considered present when increased enteric loss of α_1 -antitrypsin was documented or the clinical syndrome of PLE was present (persistent or intermittent edema with hypoproteinemia without evidence for deficient protein production or excessive protein loss from organ systems other than the gastrointestinal tract).

To identify factors associated with development of PLE, we analyzed several preoperative, perioperative, and postoperative factors. Preoperative factors included calendar year of operation, age at operation, type of anatomic defect, ventricular anatomy, presence of preoperative arrhythmia, estimate of ventricular systolic function by echocardiographic or angiographic methods, measured ventricular end-diastolic pressure, total pulmonary resistance, and pulmonary arteriolar resistance. Perioperative and postoperative factors analyzed included length of cardiopulmonary bypass, need for atrioventricular valve surgery at the time of the Fontan operation, need for early reoperation for any reason, right and left atrial pressures at the end of the operation, postoperative arrhythmias, postoperative renal failure, and length of stay in the hospital after the operation. For survival analysis, time zero was the thirtieth postoperative day, whether or not the patient was still hospitalized.

These factors were analyzed among all 30-day survivors. In addition, we assessed survival subsequent to the development of PLE by standard univariate and multivariate analyses previously described by Driscoll and associates.¹⁰ Two-tailed *p* values ≤ 0.05 were taken as evidence of findings not attributable to chance.

Results

A total of 427 patients were identified as eligible 30-day survivors. These included 260 male and 167 female patients. Basic cardiac anatomic types were distributed as follows: tricuspid atresia, 148 patients; univentricular heart, 138; and other complex cyanotic lesions, 141. The survival curve for all 30-day survivors shows that the 10-year survival of these patients was 77% (Fig. 1).

Forty-seven of the 427 patients had sufficient data to fulfill the diagnostic criteria for PLE, for a cumulative risk at 10 years of 13.4%. The onset of PLE after the Fontan operation ranged from 2 months to 9 years (mean 3.7 years). In 14 of these 47 patients (30%), PLE developed more than 5 years after the Fontan operation. The onset of PLE was associated with the development of fluid accumulation such as pleural effusion, ascites, or peripheral edema. Often no recognizable gastrointestinal symptoms were present. Only two of 47 patients reported significant change in frequency of bowel movements. A significant growth delay was noted in three patients, and the onset of puberty was considered to have been delayed in one patient.

Current status of patients with PLE. The 5-year survival after diagnosis of PLE was 46% (Fig. 2). Survivorship was not related to length of time between operation and onset of PLE. Among the 20 current survivors, four patients are in remission.

Fig. 2. Survival curve after diagnosis of PLE in patients who have had the Fontan operation.

Table I. Postoperative hemodynamic findings for patients with PLE

Variable	No.	Mean	Range
Mean right atrial pressure (mm Hg)	45	18.2	8-30
Mean pulmonary artery pressure (mm Hg)	41	18.7	8-41
Cardiac index (L/min per square meter)	29	2.3	1.4-3.7
Ejection fraction (%)	18	53.2	16-69
Total pulmonary resistance (μm^2)	31	4.5	0.8-9.9
Pulmonary arteriolar resistance (μm^2)	27	1.8	0.4-5.6
Ventricular end-diastolic pressure (mm Hg)	42	14.8	5-32
Mean wedge pressure (mm Hg)	7	11	3-17

One patient had transient PLE coincident with a *Salmonella* intestinal infection. Another has been in remission for 3 years after cardiac transplantation. One patient is currently in remission coincident with the placement of a sequential atrioventricular pacemaker for intermittent bradycardia. Another patient currently is in remission after having had PLE from 1979 until 1991. This patient derived significant clinical benefit after moving from high altitude (Denver) to sea level (San Diego).

Four current survivors have mild PLE that is reasonably well controlled by standard anticongestive measures. These patients remain active and are able to take part in normal day-to-day activities.

Their exercise intolerance is considered mild to moderate. Eight patients have PLE and are on anticongestive therapy regimens and require periodic albumin infusions. These patients have definite exercise intolerance (New York Heart Association class II). Four others currently have severe PLE coincident with significant disability (New York Heart Association class III). Two are awaiting cardiac transplantation and two others have refused that option.

Laboratory data from current PLE survivors includes total serum protein values ranging from 3.0 to 5.9 gm/dl (mean 4.3 gm/dl) and serum albumin values ranging from 1.3 to 4.0 gm/dl (mean 2.6 gm/dl). Serum calcium values range from 4.5 to 9.5 mg/dl. The patient with the lowest calcium value manifested tetany. Six patients had 24-hour α_1 -antitrypsin clearances ranging from 46.4 to 584.0 ml/day (mean 265 ml/day). Normal clearance has been determined to be less than 27 ml/day. Lymphocytopenia is common (range 2% to 46% lymphocytes, with a mean of 15% lymphocytes in the peripheral smear).

Hemodynamic findings. In an effort to better understand the hemodynamic derangement associated with PLE, we tabulated the results of cardiac catheterization or echocardiographic studies (or both) (Table I). Included were data from postoperative studies coincident with the development of PLE, irrespective of current vital status. The factors measured show wide ranges of variability, with the tendency for increased right-sided filling pressures, decreased cardiac index, increased pulmonary resis-

tance, and increased ventricular end-diastolic pressure. Estimated ventricular ejection fractions were decreased (mean 53%). Patients underwent cardiac catheterization during hospitalization for treatment of edema, fluid accumulation, and congestive heart failure. They were considered to be in reasonably stable cardiopulmonary states at the time of their catheterization.

Clinical management strategies. For those patients who are in remission, treatment has not been continued. Of those with PLE who survive, 17 of 20 (85%) are on regimens that include sodium restriction. Dietary modification, as has been advocated for the treatment in children with intestinal lymphangiectasia from other causes,^{11, 12} has been tried on four patients but none continued these dietary measures on a long-term basis.

Nineteen of 20 survivors of PLE (95%) are receiving digoxin and diuretics. Although the reinstitution of these anticongestive measures had a significant clinical effect and often was associated with a dramatic decrease in enteric protein loss, the patients continue to have PLE. Twelve of 20 patients (60%) are being treated with afterload-reducing agents in their regimen, with similar partial benefit.

Nine of 20 patients (45%) have required periodic albumin infusion that is often given before intravenous administration of furosemide therapy. For the patient with marked edema and hypoproteinemia, the benefits can be dramatic. The duration of benefit is variable and not predictable. Three patients have had courses of corticosteroid therapy given in therapeutic doses for adequate trial periods. None of these patients derived any benefit from such therapy.

Death and PLE. Of the 96 30-day survivors who have subsequently died during follow-up, 27 (28%) were patients in whom PLE had developed. Reoperation during follow-up for whatever reason is associated with high perioperative mortality among patients with PLE. Nine of 12 patients with PLE died in connection with their reoperation. Two of the deaths at reoperation occurred in patients undergoing transplantation. These two patients were believed to have long-standing congestive heart failure and had marked nutritional debilitation. All other deaths were attributed to deteriorating ventricular function and congestive heart failure.

Univariate analysis of factors associated with development of PLE. Factors not associated with development of PLE included calendar year of the

Fontan procedure, sex of the patient, preoperative ejection fraction (echocardiography or angiography), presence of preoperative arrhythmia, preoperative mean pulmonary artery pressure, and preoperative total pulmonary resistance or pulmonary arteriolar resistance (Table II). Factors associated with development of PLE included ventricular anatomy other than dominant left ventricle and increased preoperative ventricular end-diastolic pressure. Patients with tricuspid atresia were less likely to have PLE develop than patients with other types of defects (Table II).

Perioperative factors associated with development of PLE (Table II) included longer cardiopulmonary bypass time, increased left atrial pressure after the operation, longer length of hospital stay, and presence of postoperative renal failure. Postoperative renal failure was considered present when the patient needed renal or peritoneal dialysis. Early reoperation for any reason was also associated with later development of PLE.

From analysis of continuous variables (P_c in Table II), higher total pulmonary resistance, higher preoperative ventricular end-diastolic pressure, higher mean left atrial pressure after the Fontan operation, longer cardiopulmonary bypass time, and longer hospital stay were associated with the development of PLE.

Multivariate analysis. From Cox proportional-hazards modeling, the sole preoperative variable associated with later development of PLE was ventricular anatomy other than dominant left ventricle (P_m in Table II). Of perioperative variables similarly analyzed, length of hospital stay also predicted PLE development. The most significant factor predictive of PLE was the presence of renal failure in the postoperative period. PLE ultimately developed in nine of 39 such patients. A curve of probability of remaining free of PLE for those who had renal failure (Fig. 3) demonstrates that PLE often developed early in the postoperative course and the rate may level off after 5 postoperative years.

Multivariate analysis showed that the most favorable outcome (lowest risk for development of PLE) occurs in patients with a dominant left ventricle, short hospital stay (less than 15 days), and no postoperative renal failure. PLE has developed in 11 of 154 patients (7%) in this group thus far. The probability curve for surviving free of PLE for this group also demonstrates the more favorable outcome (Fig. 4).

Table II. Univariate and multivariate assessment of factors associated with development of PLE among 427 30-day survivors of the Fontan operation*

Factor	No.	Cumulative risk of PLE (%)					Pu	Pc	Pm
		Time 0	6 mo	1 yr	5 yr	10 yr			
Overall group	427	0.0	0.5	1.0	8.7	13.4	—	—	—
Preoperative factors									
Basic anatomy							0.020 (5.4)	—	NS
TA	148	0.0	0.7	0.7	3.7	8.0			
Univentricular complex	279	0.0	0.4	1.2	11.5	16.4			
Ventricular anatomy							0.010 (6.7)	—	0.021
LV	306	0.0	0.3	0.3	6.1	10.4			
All others	103	0.0	1.0	2.1	17.1	20.3			
Age at Fontan (yr)							NS	NS	NS
<4	38	0.0	0.0	0.0	9.4	9.4			
≥4	389	0.0	0.5	1.1	8.6	13.7			
Preoperative arrhythmia							NS	—	NS
Absent	395	0.0	0.5	1.1	8.7	13.7			
Present	32	0.0	0.0	0.0	8.7	8.7			
LV ejection fraction (%)							NS	NS	—
Normal (≥50)	138	0.0	0.0	0.0	8.2	10.2			
Abnormal (<50)	52	0.0	2.1	4.3	10.1	15.0			
Mean PA pressure (mm Hg)							NS	NS	—
Normal (<30)	330	0.0	0.6	1.0	9.5	14.4			
Abnormal (≥30)	34	0.0	0.0	0.0	3.8	8.2			
Pulmonary arteriolar resistance (μm ²)							NS	NS	—
Normal (≤3)	211	0.0	0.5	1.0	9.3	15.9			
Abnormal (>3)	14	0.0	0.0	0.0	16.7	16.7			
Total pulmonary resistance (μm ²)							NS	0.017 (5.7)	—
Normal (<4)	160	0.0	0.0	0.7	7.7	11.7			
Abnormal (≥4)	101	0.0	1.0	1.0	13.2	20.7			
LV end-diastolic pressure (mm Hg)							0.034 (4.5)	0.014 (6.0)	—
Normal (≤13)	225	0.0	0.9	1.4	7.4	9.2			
Abnormal (>13)	157	0.0	0.0	0.7	11.4	18.5			
Perioperative factors									
AV surgery							NS	—	NS
No	404	0.0	0.5	1.0	8.5	13.3			
Yes	23	0.0	0.0	0.0	13.8	13.8			
Postoperative arrhythmia							NS	—	—
Absent	270	0.0	0.4	0.8	5.7	11.0			
Present	157	0.0	0.7	1.4	13.9	17.8			
Mean RAP after Fontan (mm Hg)							NS	NS	—
Normal (<20)	290	0.0	0.4	1.1	6.8	11.8			
Abnormal (≥20)	132	0.0	0.8	0.8	11.8	15.8			
Mean LAP after Fontan (mm Hg)							<0.001 (12.8)	<0.001 (13.0)	—
Normal (<12)	262	0.0	0.4	0.8	5.4	8.6			
Abnormal (≥12)	137	0.0	0.8	1.6	14.1	23.2			
Early reoperation							0.020 (5.4)	—	NS
No	353	0.0	0.6	1.2	7.5	11.7			
Yes	69	0.0	0.0	0.0	15.7	25.1			
Bypass time (min)							0.011 (6.5)	0.044 (4.1)	NS
≤120	221	0.0	0.0	0.5	5.5	8.7			
>120	206	0.0	1.0	1.6	12.3	19.0			

AV, Atrioventricular valve; LAP, left atrial pressure; LV, left ventricle; PA, pulmonary artery; RAP, right atrial pressure; TA, tricuspid atresia. Pu refers to univariate probability value from log-rank test with nonsignificance (NS) if $P_u > 0.05$. With each significant finding, the associate χ^2 statistic is in parentheses. Pc refers to univariate probability value from Cox regression model testing the association between the risk of the development of PLE and the predictor variable treated as a continuous variable. Pm refers to a two-tailed p value considering the variable in a multivariate context using both preoperative and postoperative variables. Those significant were identified by a stepwise backward elimination of the nonsignificant (NS) variables. Those variables not considered are indicated by a dash line (—).

*The end point considered in these analyses was the development of PLE. Death in patients who did not have PLE was treated as a censored observation for all these analyses.

†Number of days hospitalized of the first 30 postoperative days. Hospital stays beyond 30 days were treated as 30 days for this analysis.

Table II. *Cont'd.*

Factor	Cumulative risk of PLE (%)						Pu	Pc	Pm
	No.	Time 0	6 mo	1 yr	5 yr	10 yr			
Postoperative renal failure							<0.001 (14.1)	—	0.025
Yes	39	0.0	3.0	6.4	27.7	33.7			
No	388	0.0	0.3	0.5	7.1	11.6			
Hospital stay† (days)								<0.001 (16.7)	<0.001
≤14	190	0.0	0.0	0.0	2.2	7.4	<0.001 (11.9)		
15+	237	0.0	0.9	1.9	14.7	18.9			
≤15	206	0.0	0.0	0.0	2.5	7.3	<0.001 (18.7)		
16–29	157	0.0	0.7	2.0	14.2	17.5			
30	64	0.0	1.9	1.9	20.0	29.3			

Discussion

This report is the largest and most comprehensive study of PLE cases after the Fontan operation. The chance of PLE developing among 30-day survivors was approximately 13.4% by 10 years. Other reports in the literature have been limited by the small number of patients or the brevity of the follow-up.^{4,5} The data reported in this article show that PLE can be a late complication; therefore continued and careful follow-up of all patients who have had the Fontan operation is considered necessary to identify those in whom PLE may develop in the late follow-up period.

Diagnosis and clinical manifestations of PLE.

The diagnosis of PLE is reasonably certain for these patients. Data in the literature¹³⁻¹⁵ suggest that α_1 -antitrypsin studies accurately detect excessive loss of enteric protein and, therefore, this test remains the standard for documenting PLE. In this retrospective review involving patients operated on between 1973 and 1987, α_1 -antitrypsin data were not available for all patients. With reasonable certainty, a retrospective review could identify patients who fit the clinical syndrome of PLE. Two points are worth emphasizing. Most frequently, the onset of PLE is heralded by a new onset of pleural effusion, ascites, or peripheral edema. In the presence of hypoproteinemia and no other cause for protein loss, the diagnosis of PLE is reasonable. Changes in gastrointestinal signs and symptoms are relatively uncommon. This is in contrast to other diseases associated with PLE resulting from primary gastrointestinal disease.^{11, 16-18} The effect of protein loss on maturation has been documented in patients whose growth has been delayed as well as in one instance of delay in the onset of puberty. Similar problems have been identified for noncardiac causes of PLE.¹⁸

PLE is represented by a spectrum of severity, with a patient mortality rate of 54% by 5 years after the diagnosis. The mortality rate noted for patients with PLE has not been reported previously. The survival data for all 30-day survivors is similar to findings reported by Fontan and associates¹⁹ in 1990.

The fact that PLE can be transient suggests that other phenomena may have an effect, such as an intercurrent bacterial intestinal infection that occurred in one patient. The adverse effect of living at high altitude after a Fontan operation is suggested by the finding that the condition of one patient improved after he moved from high altitude to sea level. The improvement in the condition of one patient coincident with the use of atrioventricular sequential pacing is of interest, but this modality is still untested. PLE has developed in patients who had pacemakers placed at the time of their Fontan operation.

The laboratory manifestations of PLE (hypoproteinemia, hypoalbuminemia, hypocalcemia, and lymphocytopenia) have been observed in other forms of PLE. Despite low levels of lymphocytes, a severe infection or a septic catastrophe did not develop in any of these patients. Although periodic albumin infusions have been used, gamma globulin infusions have not been considered necessary.

Management. The fact that anticongestive measures are not curative should not discourage the physician from vigorously initiating this therapy. A tendency toward improvement in the amount of enteric protein loss has been associated with the diuresis that comes with reinstituting digoxin, furosemide, and afterload-reduction agents. Unfortunately, there is usually still excessive enteric protein loss despite initiation of therapy. A clinical management strategy of periodic albumin infusions with

Fig. 3. Curve of probability of remaining free of PLE for the 39 patients who had renal failure after their Fontan operation. *Numbers in parentheses* are survivors free of PLE at 5 and 10 years. Time zero is 30 days after the Fontan operation.

intravenous administration of furosemide has been judged clinically effective for some patients and, in those who have stable ventricular function and other hemodynamic factors, has been used for extended periods without negative sequelae. The long-term use of dietary changes other than sodium restriction has not been successful for this group of patients. Part of management should include frequent follow-up visits with serial measures of serum proteins and α_1 -antitrypsin stool concentrations. Serial echocardiographic studies to monitor ventricular function have also been done.

Hemodynamic findings for patients with PLE.

The hemodynamic findings in patients who had cardiac catheterization coincident with development of PLE demonstrate increased right-sided pressures, decreased cardiac output, decreased ventricular systolic function, and abnormal ventricular diastolic function as measured by end-diastolic pressure or mean wedge pressures. Comparisons between hemodynamic findings for this group of patients and for other patients who are 30-day survivors without PLE would be distorted by the fact that the only patients having catheterization were those in whom hemodynamic derangement was suspected. Furthermore, these patients represented a clinical spectrum of severity, and protocols such as fluid challenge were not used during this period.

These data do describe the hemodynamic abnormalities seen for the first time in patients with PLE, however. The relative importance of one hemodynamic variable and PLE could not be identified.

The experience at the Mayo Clinic with use of corticosteroids in patients with PLE has not been favorable. Barber (Barber G, New York University Medical Center, personal communication) has noted a subgroup of patients with PLE after the Fontan operation who, at cardiac catheterization, have relatively normal right-sided pressures. He believes that these patients should have an intestinal biopsy and, if a cellular infiltrate is noted on biopsy, may respond favorably to corticosteroid therapy. In the patients in the present study, low right-sided pressures were infrequent and none had received corticosteroid therapy.

Although cardiac transplantation has been used infrequently in the past, it is the option that may be considered for patients who have PLE associated with deteriorating hemodynamic variables and poor response to anticongestive measures. If transplantation is considered, it should be undertaken before nutritional debilitation is manifest. The role of creating a right-to-left shunt at the atrial level as a method of treating PLE has been used on too few patients to reach a conclusion about this strategy. However, a recent report has suggested benefit from

Fig. 4. Curve of probability of remaining free of PLE for the 154 patients with a dominant left ventricle whose hospital stay was less than 15 days and who did not have renal failure after the Fontan operation. Numbers in parentheses are survivors free of PLE at 5 and 10 years. Time zero is 30 days after the Fontan operation.

that approach.²⁰ Theoretically, lowering right atrial pressure might result in clinical improvement of PLE provided that other measures of cardiac function are adequate and stable.

Factors associated with development of PLE. The finding of significant preoperative and perioperative factors associated with later development of PLE resulted from statistical methods similar to the one reported by Driscoll and associates.¹⁰ This series looked only at 30-day survivors and included a longer operative experience. Similarities in mortality risk noted by Driscoll's group¹⁰ and results in this report are not surprising. Unfavorable preoperative factors included defect other than tricuspid atresia, ventricular anatomy other than dominant left ventricle, increased ventricular end-diastolic pressure, and increased total pulmonary resistance. These findings clearly emphasize the need to be scrupulous in selecting patients for the Fontan operation. Unfavorable perioperative factors included prolonged duration of cardiopulmonary bypass, increased postoperative left atrial pressure, postoperative renal failure, and increased duration of postoperative hospital stay. It was not possible to analyze other potential postoperative risk factors for PLE, such as duration of pleural effusions, because of the aggressive and highly

effective use of chemical and mechanical pleurodesis during this period. The presence of one or more of those unfavorable variables should help alert the clinician to the possible increased risk of PLE occurring later in the patient's postoperative course.

This retrospective review includes patients operated on with techniques for the Fontan operation used before February 1, 1987. Since that time direct cava-pulmonary artery connections, lateral atrial tunnel, and similar techniques have been introduced. Short-term mortality rates after the Fontan operation have declined steadily since 1987.²¹ This improvement may well result from a combination of better case selection and improved surgical techniques. It remains to be seen whether experience since 1987 is associated with a lower rate for PLE development during the postoperative course. Because PLE may be a late complication, follow-up of at least 5 years is needed to assess the effects of newer operative techniques on incidence of this complication.

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