



Predictors of prolonged pleural effusion after Fontan operation

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Abstract

Prolonged pleural effusion is a fairly common condition which has considerable impact on complicated and longer hospital stays after Fontan surgery. Identifying the patient population prone to have pleural effusions is still seeking for an answer. This study is to determine the variables that may predict prolonged pleural effusion according to the data of 69 patients who underwent Fontan operation between June 2018 and December 2020 and survived to date. Prolonged pleural effusion was defined as the need for a chest tube for more than 7 days. Two patient groups, *with* and *without* prolonged effusion, were compared in terms of pre-, peri-, and post-operative variables. The patients were subdivided into "high-risk" and "low-risk" groups based on the pre-operative catheterisation data. The most frequent main diagnosis was tricuspid atresia (n: 13, 19%). Among 69 patients, 28 (40%) had prolonged pleural effusion whereas 11 (16%) had effusions that lasted longer than 14 days. Ten patients among prolonged effusion group (35%) had pulmonary atresia coexistent with the main diagnosis. Fontan operation was performed in 6 patients (8.7%) over the age of 10, and 4 of these patients (67%) had prolonged pleural effusion. Among numerous variables, statistical significance between the two groups was achieved in pre-operative mean pulmonary artery pressure, post-operative albumin, C-reactive protein levels, length of hospital stay, duration of chest tube drainage, and amount of effusion per day. Early recognition and treatment strategies with routine medical protocol use remain to be the cornerstone for the management of post-operative prolonged pleural effusions after Fontan surgery.

The last stage of palliative surgeries for patients with a single effective ventricle, also known as "Fontan procedure," has survived to the present day with devoted and ongoing modifications since the 1970s to reduce both mortality and morbidity. The creation of a total cavopulmonary connection enabled many children with fatal defects to live into adulthood. Even though mortality has improved, non-physiological flow dynamics constituted the remaining problems related to morbidity. By the advances in surgical technique and patient follow-up since the first Fontan operation, the current interest is not to ensure the survival of patients, but to increase their quality of life after surgery. Among morbidities, prolonged pleural effusion following the Fontan operation is the most common complication that is responsible for increased length of hospital stay and increased time with draining tube thoracostomies. More importantly, prolonged pleural effusion, which manifests in the early post-operative period, may be a precursor of a failing Fontan circulation that may consequently cause the eruption of other "hard-to-cope-with" entities such as plastic bronchitis, protein-losing enteropathy, thromboembolism etc.^{1–3} For these reasons, determining appropriate candidacy for "ideal" Fontan operation and predicting patients who will experience a problematic post-operative course is crucial. In our institution since 2018, a medical treatment protocol, which resulted to be effective in terms of decreasing the total drainage, duration of pleural effusion, and length of hospital stay, applied to all patients immediately after Fontan operation.⁴ The purpose of this study is to enlighten the factors (among numerous pre-operative, operative, and post-operative variables) affecting the effusion by reviewing the data of patients whose hospitalisation was complicated by prolonged pleural effusion despite the protocol.

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Materials and method

Patient group and data

The medical data of 69 patients who underwent Fontan operation for the end-stage palliation of single ventricle physiology at Mehmet Akif Ersoy Training and Research Hospital between June 2018 and December 2020 and survived were reviewed. The study was approved by the review board of our institution. We analysed baseline characteristics, pre-operative clinical data, haemodynamic data from cardiac catheterisation, operative, and post-operative variables in all patients (146 variables). The study period was started from June 2018 which is the date we initiated a modified protocol of ours that was applied to all patients immediately after Fontan operation (Table 1). Prolonged pleural effusion was defined as the need for a chest tube for >7 days despite the protocol (prolonged pleural effusion group and non-prolonged pleural effusion group). We compared data between the two groups. All candidates were routinely evaluated with cardiac catheterisation in our institution prior to Fontan operation, and the following data were collected: pulmonary vascular resistance, systemic vascular resistance, mean pulmonary artery pressure, end-diastolic pressure of the systemic ventricle, and transpulmonary gradient. We also checked the distribution and calibration of the pulmonary arteries with Z-scores, pulmonary venous return; the systemic and hepatic venous return, bidirectional Glenn anastomosis, systemic outflow obstruction, aortopulmonary or veno-venous collaterals; and pulmonary arterio-venous fistulae. For the purpose of revealing risk factors associated with prolonged pleural effusion based on catheterisation data, patients were subdivided into “high-risk” and “low-risk” groups (high risk is defined by either of pulmonary vascular resistance/ systemic vascular resistance >0.3, mean pulmonary artery pressure >15 mmHg, end-diastolic pressure of the systemic ventricle >12 mmHg, transpulmonary gradient >10 mmHg, right pulmonary artery or left pulmonary artery Z-score <−2.00). Patients with elevated mean pulmonary artery pressure and/or pulmonary vascular resistance/systemic vascular resistance ratio as mentioned above are treated with a pulmonary vasodilator, typically sildenafil± bosentan, and are reassessed with cardiac catheterisation after 6–12 months of treatment.

Surgical technique

The extracardiac Fontan operation was routinely performed for end-stage palliation in all patients, and an intra-extracardiac Fontan operation was performed in patients with isomerism and unusual systemic and pulmonary venous patterns. The procedures were performed under normothermic or mild hypothermic cardiopulmonary bypass. Cardioplegic arrest was used only in cases of concomitant intracardiac procedures. The pulmonary arteries were reconstructed as necessary. All remaining pulmonary antegrade flow was occluded at the Fontan operation, if not previously. Fenestration is performed in cases with moderate or severe atrioventricular valve regurgitation or high pulmonary vascular resistance, end-diastolic pressure of the systemic ventricle, and cases with comparably older age at Fontan operation. For eligible patients, a 4 mm fenestration was created in the conduit.

Post-operative follow-up

For ICU follow-up, our institutional routine is to extubate the patient as early as possible, apply low positive end expiratory pressure, if the patient remains intubated, and maintain a positive fluid balance for the first 24 hours to assure a fully loaded Fontan system

Table 1. Istanbul Mehmet Akif Ersoy Training and Research Hospital, Fontan protocol (modified Wisconsin protocol).

Post-operative 6th hour, heparin initiated (infusion rate of 15 U/kg/h) if there was no bleeding (ceased at post-operative 1st day).
Post-operative 1st-day enoxaparin (1 mg/kg/d) initiated (single dose/d, ceased at discharge).
Post-operative 1st-day intravenous (iv) furosemide (1 mg/kg/d) initiated (switched to perioral (po) furosemide [1 mg/kg/d, two divided doses] after the drains were removed).
Lisinopril 0.1 mg/kg/d (po, single dose).
Spirolactone 1 mg/kg/d (po, two divided doses).
Aspirin 5 mg/kg/d (po, single dose).
Sildenafil 3 mg/kg/d (po, three doses).
0.5 L/min nasal oxygen supply until the drains were removed.
Fluid restriction (80% of daily fluid requirement).
Low-fat diet (30% of daily calories from fat).
Chest tubes were removed when drainage decreased to 2 ml/kg/d.
If the need for drainage exceeded 1 wk, fat was withdrawn from the diet except for medium-chain triglycerides.
If drainage continued, oral feeding was ceased and total parenteral nutrition was initiated.
Catheter angiography was used to detect and correct the residual pathologies if the need for ongoing drainage exceeds 14 d or if it was necessary to create a transcatheter fenestration in the case of high Fontan pressure without a residual pathology.

which is a passive conduit. At immediate post-operative period, we applied the aforementioned protocol.^{5,6} Chest tubes were removed if the drainage converts into serous character, chest X-ray demonstrating no significant pleural collection, and drainage was <2 ml/kg/day. A delicate diet was applied to patients if the pleural drainage prolonged and exhibited chylous character, fat was withdrawn from the diet except for medium-chain triglycerides, and total parenteral nutrition was initiated if chest tubes were not withdrawn in the post-operative 14 days. Catheter angiography was performed if the drainage period exceeded 14 days and total parenteral nutrition brought no help. Octreotide use was preserved for cases with substantial and prolonged chylous output. We continued the low-fat diet for 6 weeks after removal of the last chest tube.

Statistical analysis

Data analyses were performed using SPSS 25 software and were presented as median values (and range). The χ^2 test was used for categorical variables, and the unpaired Student's t-test was used for continuous variables that were distributed normally. Non-parametric continuous variables were analysed using the Wilcoxon rank-sum test/Mann-Whitney U-test. Univariate analysis was performed for possible variables to predict prolonged pleural effusion. Those variables with a p value <0.05 were considered to be statistically significant.

Results

Pre-operative variables

Baseline characteristics of the patients are displayed in Table 2. In detail, 40 patients were female (58%), the median age at Fontan

Table 2. Pre-operative demographic data.

Pre-operative variables (median values and range are provided)	All patients (n:69) n/ (%)	Non-PPE group (n:41)	PPE group (n:28)	p value
Age at Fontan operation (year)	4.9 (2.5–26)	5 (2–26)	5 (3–15)	0.75
Age at Glenn shunt (month)	18.9 (2–76)	11 (2–76)	12.5 (2–75)	0.57
Age at Kawashima operation (month)	26 (8–72)			
Glenn shunt to Fontan operation interval (year)	4.7 (1–13)	4 (1–10)	3.7 (1.1–13)	0.49
Weight (kg)	16.6 (12.5–57)	16.25 (12.5–57)	17 (13–37)	0.88
Gender (n, %)		0.6		
Female	40 (58)	26 (37)	14 (20)	
Male	29 (42)	14 (20)	15 (22)	
Diagnosis (n, %)		0.48		
TA	13 (19)	12 (17)	1 (1.5)	
AVSD + DORV	11 (16)	7 (10)	4(5)	
DORV	11 (16)	6 (8)	5 (5.5)	
IVS-PA	10 (14)	5 (5.5)	5 (5.5)	
U-AVSD	7 (10)	5 (5.5)	2 (3)	
CC-TGA	6 (8)	1 (1.5)	5 (5.5)	
DILV	5 (5.5)	2 (3)	3 (4)	
TGA	2 (3)	1 (1.5)	1 (1.5)	
DOLV	2 (3)	1 (1.5)	1 (1.5)	
HLHS	1 (1.5)	0	1 (1.5)	
EBSTEIN	1 (1.5)	0	1 (1.5)	
Dominant Ventricle (n, %)		0.8		
Left	39 (56)	24 (35)	15 (22)	
Right	21 (30)	12 (17)	9 (13)	
Balanced with remote VSD	9 (13)	4 (5)	5 (5.5)	
Situs (n, %)		0.62		
Solitus	46 (67)	25 (36)	21 (30)	
Right atrial isomerism	10 (14)	6 (8)	4(5)	
Inversus	7 (10)	4(5)	3 (4)	
Left atrial isomerism	6 (8)	5 (5.5)	1 (1.5)	
TAPVD (n, %, type)	4(5)	3 (4) (2 supracardiac and 1 cardiac non-obstructive)	1 (1.5) (supracardiac obstructive)	

(Continued)

Table 2. (Continued)

Pre-operative variables (median values and range are provided)	All patients (n:69) n/ (%)	Non-PPE group (n:41)	PPE group (n:28)	p value
AVVR (n, %)		0.32		
None	21 (30)	13 (19)	8 (11)	
Mild	28 (40)	17 (25)	11 (16)	
Moderate	18 (26)	9 (13)	9 (13)	
Severe	2 (3)	1 (1.5)	1 (1.5)	
Systemic outflow obstruction (n)	2 (3)	1 (1.5)	1 (1.5)	
Systemic ventricular dysfunction (n)	0			
sPO2 (%)	82 (50–90)	81 (74–89)	82 (50–90)	0.57
Haematocrit (%)	45 (28–69)	45.5 (39–57.5)	45 (28–69)	0.46
Catheterisation data				
PAP (mmHg)	11 (6–19)	11 (6–19)	14 (8–19)	0.015
TPG (mmHg)	5 (1–13)	5 (1–10)	5 (2–13)	0.91
EDP (mmHg)	7 (2–15)	6.5 (2–15)	7.5 (5–15)	0.1
LPA (mm)	8.8 (4.1–25.3)	8.85 (4.1–21.8)	9.1 (5–25.3)	0.86
RPA (mm)	10 (5.4–26.7)	10 (5.4–23.6)	10.05 (6.4–26.7)	0.6
McGoan ratio	2.12 (1.31–4.5)	2.26 (1.7–4.5)	2 (1.31–3.7)	0.6
Nakata (mm ² /m ²)	244.5 (100–1275)	242.5 (116–692)	282.5 (100–1275)	0.4
PVR-SVR	0.15 (0.02–0.24)	0.1 (0.02–0.29)	0.1 (0.02–1)	0.32
At least one “high-risk” variables (n, patients)	19 (most common is high PAP)	7	9	
Interventions needed before Fontan (n)	16	8	7	

Abbreviations: TA, tricuspid atresia; u-AVSD, unbalanced atrioventricular septal defect; DORV, double outlet right ventricle; IVS-PA, intact ventricular septum-pulmonary atresia; cc-TGA, corrected transposition of great arteries; DILV, double inlet left ventricle; TGA, transposition of great arteries; DOLV, double outlet left ventricle; HLHS, hypoplastic left heart syndrome; VSD, ventricular septal defect; TAPVD, total abnormal pulmonary venous return; AVVR, atrioventricular valve regurgitation; PAP, mean pulmonary artery pressure; TPG, transpulmonic gradient; EDP, systemic ventricular end-diastolic pressure; LPA-RPA, left and right pulmonary arteries; PVR-SVR, pulmonary and systemic vascular resistance.

operation was 4.9 years (range 2.5–26), and the most frequent main diagnosis was tricuspid atresia (n:13, 19%). Ten patients among prolonged pleural effusion group (35%) had pulmonary atresia coexistent with the main diagnosis. Dominant ventricle was left in 39 (56%), and total anomalous pulmonary venous drainage

was observed in 4, mostly supracardiac and concomitantly in patients with right atrial isomerism and right ventricular dominance (6%). Among those 4 patients with total anomalous pulmonary venous drainage, only one patient had prolonged pleural effusion. Only 1 of 6 patients with left atrial isomerism (17%) had prolonged pleural effusion and prolonged for more than 14 days. Atrioventricular valve regurgitation figures before Fontan operation were as follows: the most common was mild regurgitation in 28 of all patients (40%) and in 11 of patients (39%) suffering from prolonged pleural effusion. No statistically significant difference was found between two groups in terms of atrioventricular valve regurgitation. The median age at Glenn shunt operation was 18.9 months (2-76), and age at Glenn shunt surgery was not found to be a risk factor for having prolonged pleural effusion when patients were further divided into 3 subgroups according to their age at Glenn shunt operation (4–6 m, 6–12 m, 12 m<)(p:0.57).

The median time interval from Glenn shunt to Fontan operation was 4.7 years (1–13 years) in the entire cohort and was not significantly different between prolonged pleural effusion and non-prolonged pleural effusion groups. Fontan operation was performed in six patients (8.7%) over the age of 10, and 4 of these patients (67%) had prolonged pleural effusion, whereas in two patients prolonged pleural effusion lasted longer than 14 days. Two patients had systemic ventricular outflow tract obstruction, none of whom had prolonged pleural effusion after Fontan operation. Systemic ventricular functions were preserved in all patients pre-operatively. Median saturation and haematocrit values were 82 and 45%, respectively. Laboratory indices were within the normal range in two groups before Fontan operation and deviations from initial pre-operative values are covered in post-operative data part comparably. As for catheterisation data, the median mean pulmonary artery pressure was 11 mmHg (6–19) and the median transpulmonary gradient was 5 mmHg (1–13). *Pre-operative mean pulmonary artery pressure was elevated in prolonged pleural effusion group (p:0.015)*. Other catheter derived data were shown in Table 2. The most common angiographically obtained “high-risk” factor was elevated mean pulmonary artery pressure (four patients-13%) in prolonged pleural effusion group, and in two patients, both of whom had more than one risk factor, pleural effusion lasted longer than 14 days. Among all, 21 patients (30%) had prolonged pleural effusion despite having no risk factor at all. Seven patients out of 11 (70%) with effusion lasted more than 14 days had no risk factor. Anti-pulmonary hypertension treatment was initiated in six patients (three of whom had prolonged pleural effusion) as the mean pulmonary artery pressure was more than 15 mmHg in the pre-Fontan catheter. Ten patients (15%), none of whom had prolonged pleural effusion, required 16 interventions at diagnostic angiography before Fontan operation (five veno-venous collateral occlusions and four major aortopulmonary collateral artery occlusions being the most common). Pre-operative stage 1 preferences and concomitant procedures are listed in Table 3, and palliation preferences were not statistically associated with prolonged pleural effusion. Nevertheless, no connection could be established in terms of prolonged pleural effusion, presence of collaterals requiring transcatheter intervention, and pulmonary artery Z-scores at pre-operative catheterisation between the group whose antegrade pulmonary flow was occluded at the Glenn shunt stage and the group that was not (p:0.34 for prolonged pleural effusion, p: 0.7 for fistula occlusion, p: 0.5 for z-scores).

Table 3. Initial palliation references at Stage 1 and Stage 2 (Glenn shunt) data.

Type of palliation (n of procedures)	All patients (n:69)	Non-PPE group (n:41)	PPE group (n:28)
None	21	11	10
Shunt (central / Blalock-Taussig)	20	12	8
Pulmonary artery banding	13	8	5
Patent ductus arteriosus stenting	13	10	3
Balloon atrial septostomy	8	6	2
RVOT stent	1	0	1
Norwood	1	0	1
Vertical vein stenting	1	1	0
Unilateral Glenn shunt (n)	53	32	21
Bilateral Glenn shunt (n)	16	9	7
Concomitant interventions at Glenn stage (n of procedures)			
None	22	10	12
Pulmonary artery reconstruction	13	9	4
Atrial septectomy	10	8	2
Pulmonary antegrade closure	4	3	1
AVV repair	4	4	0
TAPVD repair	3	2	1
Arcus reconstruction	1	1	0
Pacemaker implantation	1 (for sinus node dysfunction)	1	0

Abbreviations: RVOT, right ventricular outflow tract; AVV, atrioventricular valve; TAPVD, total abnormal pulmonary venous return.

Operative and peri-operative data

Extracardiac Fontan operation was applied to all except seven patients who underwent intra-extracardiac Fontan. Fenestration was performed in six (8%) patients during the procedure, three of whom had prolonged pleural effusion post-operatively. There was no statistically significant difference between the groups in terms of cardiopulmonary bypass, fenestration rate, and aortic cross-clamp time. Thirty-six (52%) patients underwent an additional concomitant procedure during the Fontan surgery. Atrioventricular valve repair was the leading procedure ($n = 9$, 13%), which was followed by pulmonary artery reconstruction ($n = 6$, 8%), whereas 33 patients (48%) did not need any additional manipulation (Table 4). Among 69 patients, 28 (40%) had prolonged pleural effusion, whereas 11 (16%) had effusion that lasted longer than 14 days. Post-operative extubation was at median of 6 hours (1–26). The median post-operative ICU stay and hospital stay were 3 days and 10 days, respectively. Other post-operative variables comparable to both groups are provided in Table 4. [Among numerous variables, statistical significance between the prolonged pleural effusion and non-prolonged pleural effusion

Table 4. Operative and post-operative data.

Fontan type	All patients (n:69)	Non-PPE group (n:41)	PPE group (n:28)	p value
Extracardiac	62	35	27	
Intra-extracardiac	7	4	3	
Fontan tube size (mm)	19 (16–24)	19 (16–24)	19 (16–20)	0.75
Peri-operative SCV/ICV/RA (mmHg)	10 (5–16)/ 10 (5–16)/ 4 (0–10)	10 (5–14)/10 (5–15)/ 4 (0–10)	10 (7–16)/10 (6–16)/ 4 (0–8)	0.9/0.94/0.1
CPB time (min)	89 (56–230)	88 (60–230)	89 (56–173)	0.76
ACC time (min)	41 (5–127)	23 (5–127)	48 (5–66)	0.6
Concomitant interventions (n of procedures)				
None	33	16	17	
AV valve repair	9	5	4	
Pulmonary artery reconstruction	6	4	2	
Fenestration	6	3	3	
ASD enlargement	4	1	3	
VSD enlargement	1	0	1	
Relief of LVOTO	1	0	1	
Pacemaker implantation	1 (for post-operative AV block)	0	1	
Extubation (hour)	6 (1–26)	6 (1–18)	6 (2–26)	0.714
Fluid balance in the PO first day	680 (18–2800)	635 (18–2260)	780 (90–2800)	0.62
Post-operative early CVP (mmHg)	13 (6.6–20.6)	13 (8–20.6)	14.7 (6.6–19)	0.38
Early/late sPo2	92 (78–98)/ 95 (73–98)	92 (78–98)/ 94 (73–98)	92 (85–98)/ 95 (80–98)	0.91/0.49
Early/late laboratory indices*				
Albumin (gr/dl) (late)	3.14 (2.1–4.3)	3.4 (2.8–4.3)	3.1 (2.2–3.9)	0.014
CRP (early)	60 (14–226)	40 (14–226)	70 (18–150)	0.04
CRP (late)	30 (5–352)	23.5 (5–40)	63 (40–352)	<0.001
GGT (late)	24 (14–160)	27 (10–55)	33 (10–160)	0.04
Duration of ICU stay (day)	3 (1–46)	3 (2–20)	4 (1–46)	0.55
Amount of effusion (ml/day)	160 (10–1080)	81.8 (10–375)	101 (50–1080)	<0.001
Transcatheter intervention during hospital stay	6	0	6	
Early readmissions (within PO 30 days)	13	6	7	
Long-term complications of Fontan	6	2	4	

Abbreviations: SCV, superior caval vein; ICV, inferior caval vein, RA, right atrium; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; VSD, ventricular septal defect; ASD, atrial septal defect, CRP, C-reactive protein; GGT, gamma-glutamyl transferase.

*: “early” represents the post-operative day 0 to 3, “late” represents follow-up interval in the patient ward. Only statistically significant laboratory indices were provided.

groups was achieved in pre-operative mean pulmonary artery pressure; post-operative albumin, C-reactive protein and gamma-glutamyl transferase levels, and amount of effusion per day].

Catheter angiography was performed in all patients with an extraordinary post-operative clinical course such as failure of extubation, prolonged effusions, unexplained hypotension, desaturation, or decreased contractility of single ventricle. Six patients required catheter angiography within the post-operative 30 days [two diagnostic purposes, three transcatheter fenestration (one due to spontaneous closure of surgical fenestration) and one fenestration closure due to ischaemic cerebrovascular event].

Readmissions within post-operative 30 days were due to recurrent pleural effusion for 8 patients (all were managed medically), surgical site infections treated with intravenous antibiotics for 2, supraventricular arrhythmia that needed cardioversion for 1,

ascites that was later complicated by protein-losing enteropathy for 1. One patient, who had bilateral bidirectional Glenn shunt operation at 6 years old, underwent Fontan operation a year afterwards with the diagnoses of right atrial isomerism, unbalanced common atrioventricular canal defect with severe atrioventricular valve regurgitation. Her post-operative period was complicated with intractable bilateral pleural effusion that required initial thoracic duct ligation which resulted inconclusively and sclerosing agent administration therapy to lymph nodes afterwards.

Discussion

Despite the mortality following Fontan operation has being reduced, morbidity remains considerable. Real cause of persistent effusions is obscure and likely multifactorial. We apply a medical

treatment protocol that was reported to reduce amount of total pleural drainage in the immediate post-operative period after Fontan procedure since 2018.⁴ Nevertheless, still some patients have prolonged pleural effusion, which was the source of inspiration for the current study to uncover the risk factors for prolonged pleural effusion despite protocol. We defined effusion "prolonged" >7 days contrast to many published series that defined it as >14 days.^{7,8} Although this explains slightly elevated rate of our cohort group for prolonged effusion (%40), which is still consistent with the literature, we claim that "7 days" was a more appropriate cut-off interval for defining "prolonged" to detect and intervene problems in the Fontan circulation earlier and to reduce length of hospitalisation and susceptibility to infections.⁸⁻¹⁰

Appropriate timing for Fontan completion is associated with post-operative outcomes and prolonged effusions. Iyengar et al. from Anzac registry including 1071 Fontan patients claim that early Fontan operation does not bring superiority and later age at surgery seems to be associated with worse late functional outcomes but also worse early outcomes.² Our cohort also showed that the incidence of prolonged pleural effusion increased in patients who had Fontan operation at older age, though it did not reach a statistical significance due to limited number of patients. Surgical timing is also important at Glenn shunt stage. Although age at Glenn shunt did not differ in terms of prolonged pleural effusion, we suggest that Glenn anastomosis plays a crucial role by partially unloading the systemic ventricle and should not be performed too late once pulmonary arterial development is considered sufficient.¹¹

As for morphology, the frequency of prolonged pleural effusion has been reported to be higher in right ventricular dominant circulations or specifically in patients with hypoplastic left heart syndrome in the literature.^{2,9,12,13} Even though we had only one patient with a primary diagnosis of hypoplastic left heart syndrome, tricuspid atresia is less likely to be a risk factor for prolonged pleural effusion compared to other pathologies in the current study. From this point of view, it can be speculated that a ventricle with preserved systemic ventricular functions and congenitally programmed to support systemic circulation is a more suitable candidate for Fontan physiology. Another anatomical consideration is the competence of pulmonary vasculature to adopt total cavopulmonary anastomosis. Lo et al. claimed that pulmonary atresia was a predictor of prolonged pleural effusion which we approve by having 35% of pulmonary atresia in our patient group suffering from prolonged effusion.⁸ The underlying pathology may be the incomplete adaptation process in the postnatal period of the vascular bed that was not sufficiently perfused in the intrauterine period even though pulmonary vascular resistance calculations and pulmonary artery Z-scores were proven to be within normal range.

Atrioventricular valvular regurgitation is another concern in patients undergoing Fontan operation, with most patients having mild degree of regurgitation before surgery in both literature and in our cohort.^{7,14} Moderate to severe regurgitation status is considered for concomitant atrioventricular valve repair at surgery in our institution to preserve diastolic functions of the "long-time sufferer" ventricle though concomitant atrioventricular valve repair and pre-operative moderate/severe atrioventricular valve regurgitation were not related to prolonged pleural effusion in the present study. Tran et al. published atrioventricular valve regurgitation as a pre-operative variable for prolonged pleural effusion, and Podzolkov et al. suggested correction of moderate to severe regurgitation not after Fontan completion despite the contradictory

findings on the appropriate timing of atrioventricular valve repair in univentricular hearts.^{7,14}

New "Fontan circulation" is an altered form of haemodynamics and strictly intolerant to stenosis at any site through the vascular tubing system including pulmonary arteries, systemic ventricular outflow tract, any of which needs to be corrected before or at Fontan stage. For this reason, we prefer to perform cardiac catheterisation before Fontan operation for evaluation of aforementioned concepts. We also welcome new imaging techniques in this patient population to allow us to identify pre-operative high-grade abnormal thoracic lymphatic perfusion as a risk factor for developing early post-Fontan complications. Currently, we initiated to obtain cardiac MRI of these patients pre-Fontan routinely. Among variables extracted from catheterisation data, pre-operative mean pulmonary artery pressure, which was also the most common angiographically obtained "high-risk" factor in patients with prolonged pleural effusion, was found to be elevated in prolonged pleural effusion group and *intraoperative* measurements were found mostly within normal limits even in patients with prolonged pleural effusion and elevated mean pulmonary artery pressure at pre-Fontan catheterisation maybe due to effect of general anaesthesia on pulmonary vascular resistance. Lo rito et al. with 324 patients claimed that a 5 mmHg increment in pre-Fontan mean pulmonary artery pressure was associated with a 25% increase in the duration of chest tube requirement.⁸ Sasaki et al. reported that increased mean pulmonary artery pressure was associated with prolonged length of stay among their 218 patients.¹⁵ Therefore, though there was no absolute cut-point, a pre-operative mean pulmonary artery pressure ≥ 15 mmHg is a reliable data for early outcomes and prolonged pleural effusion as many publications support.^{3,8} Another important finding of ours that patients with more than one catheterisation "high-risk" factor had effusion lasted more than 14 days. Interestingly, among all, 30% had prolonged effusion despite having no angiographic risk factor at all. Seven patients out of 11 (70%) with effusion lasted more than 14 days had no risk factors. *To summarise, the absence of a risk factor does not exclude the possibility of early complications, whereas high mean pulmonary artery pressure in the pre-Fontan catheter can be considered as predictive of prolonged pleural effusion.*

Currently, extracardiac conduit use is becoming the preference of anastomosis in patients undergoing Fontan surgery. However, which patient should be fenestrated is still in need for consensus. Fenestration rates were similar between two groups in our study. In many previous reports, fenestration has been associated with better outcomes, including a decreased risk of death, prolonged pleural effusion, and longer hospitalisation. Lemler et al. performed the prospective randomised trial to evaluate the clinical utility of fenestration in patients with standard pre-operative risk profiles for 49 consecutive Fontan operations. They concluded that baffle fenestration improves short-term outcome in standard-risk patients by decreasing pleural drainage, length of hospital stay, and need for additional post-operative procedures.¹⁷ In our unit, we suggest that opening fenestration in risky patients would be appropriate bearing the decrease in saturation and the risk of embolic phenomena in mind.

The relationship between the course of laboratory parameters and prolonged pleural effusion in the post-operative period raised curiosity, since there are not many publications on this subject. At the same time, the opening of the pleural cavities during the operation, the subsequent inflammatory process, and the increase in

vascular permeability as a result of possible pressure changes in the lymphatic system contribute to the formation and prolongation of pleural effusion. Harmoniously, it was demonstrated that in post-operative Fontan patients, the inflammation within the pleural space, which is significantly greater when compared to controls undergoing cardiopulmonary bypass, is out of proportion to the systemic inflammation.¹⁸ Our findings indicate that post-operative albumin levels (late) were lower, whereas both early and late C-reactive protein levels were elevated in prolonged pleural effusion group. Although high C-reactive protein levels in the late period indicates ongoing inflammation and low albumin levels indicates protein wasting due to capillary leakage secondary to inflammation, considering the contribution of variables such as infection, fluid balance, blood transfusions, diuretic therapy in the post-operative period, it is debatable how much these findings can be adapted to daily practice. However, early C-reactive protein levels, post-operative 0–3 days, may be a good predictor. In this context, we postulate that inflammation and vascular permeability within the pleura and factors affecting this permeability such as cardiopulmonary bypass and infections are effective in prolonging the effusion. Moreover, providing an infection-free post-operative follow-up and to strengthen the medical treatment with corticosteroids and anti-inflammatory agents in cases without active infection are becoming prevalent in our unit. In spite of application to a small number of cases yet, the decrease in duration of effusion and hospital stay appears encouraging.

Through this study, we tried to predict prolonged effusion after Fontan surgery over conventional variables due to the retrospective design. Nevertheless, we are well aware of that in order to approach perfection in Fontan physiology innovative variables need to be involved. Methods such as computational fluid dynamics initiating the evaluation from Glenn shunt stage even possibly from the palliation period to reveal the haemodynamics in the pulmonary arteries, MRI before Fontan to evaluate lymphatic system which is of great importance and maybe utilisation of “flow study” to evaluate the pulmonary arterial vasculature readiness by simulating a Qp/Qs of 1 in the intraoperative period would be our future interests.

Conclusion

Pleural effusion after the Fontan procedure continues to be a challenging problem. Therefore, risk-stratifying patients for Fontan candidacy and implementing consistent post-operative care with a standardised protocol targeting the unique physiology of Fontan patients are crucial. Elevated pre-operative mean pulmonary artery pressure; post-operative elevated C-reactive protein; and low albumin levels were related with prolonged pleural effusion in the current study.

Limitations

This study was limited by its retrospective and single-centre design. Due to limited number of patients, multivariate model could not be constructed despite many variables being available. Although we had patients with infections or complicated with acute kidney injury during long stays in the ward, their statistical significance could not be considered due to the limited number of patients complicated with those entities.

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