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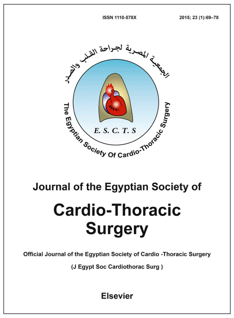

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Predictors of unfavourable early outcome following Fontan completion

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Abstract:

Background: Although the magnificent improvement in Fontan operation results in the last two decades, there are still some concerns regarding the unfavourable early outcomes that may follow Fontan completion.

Methods: From 2003 to 2016, 79 Patients underwent Fontan operation at IRCCS Policlinico San Donato. Unfavourable early outcome was defined by the presence of one or more of these occurrences: prolonged hospital stay > 25 days, Prolonged pleural effusion $\geq$ 14 days and Prolonged inotropic support $\geq$ 72 hours. Univariable and multivariable analyses were performed to detect the risk factors associated with early unfavourable outcome after Fontan completion.

Results: Prolonged hospital stay > 25 days was found in 24.05% of patients and its associated significant risk factors were low preoperative O_2 saturation (p 0.007), Fontan fenestration (p 0.009) and plasma transfusion (p 0.030). Prolonged pleural effusion $\geq$ 14 days was found in 24.05% and no significant risk factors were detected. Prolonged inotropic support $\geq$ 72 hours was found in 35.44% and significant risk factors were prolonged cardiopulmonary bypass time (P 0.003), fenestration (P 0.023), plasma transfusion (P 0.028) and non staged Fontan (P 0.039). In multivariable analysis of combined unfavourable outcome, significant risk factors were fenestration (P 0.030) with some trends towards low preoperative O_2 saturation (P 0.056).

Conclusion: Unfavourable early outcome can occur following Fontan completion with associated prolonged hospital stay. Risk factors include low preoperative O_2 saturation, prolonged cardiopulmonary bypass time, Fontan fenestration, Plasma transfusion and non staged Fontan.

(1) Introduction

Since the introduction of Fontan operation by Fontan and Baudet [1] in 1971, several modifications have been applied to it with the same basic concept of directing systemic venous return directly to the pulmonary arteries bypassing the right side of the heart.

The extracardiac conduit using Goretex tube with inferior cavo-pulmonary connection is considered the most routinely used technique for Fontan completion in these days since published by Marcelletti et al. in 1990. [2]

Thanks to the many adjustments applied to this procedure and marked improvement in the postoperative care through the last two decades, surgical results have been much improved and the incidence of mortality and early failure have markedly declined recently [3, 4, 5]

However, unfavourable postoperative morbidities are still present and several patients need prolonged length of stay after the operation. In this study we investigate risk factors associated with unfavourable early outcome after Fontan completion.

(2) Patients and Methods:

We included all patients who had Fontan procedure at IRCCS Policlinico San Donato (Milan, Italy) in 14 years from 2003 to 2016 with the exclusion of conversion of previous atrio-pulmonary anastomosis and lateral tunnel to extracardiac Fontan. Retrospective review of patients' charts, preoperative, operative and postoperative notes was conducted to collect the studied variables.

In this study prolonged length of stay was defined if more than 75 percentile (> 25 days) and prolonged pleural effusion was defined as per greater than 75 percentile after surgery ($\geq$ 14 days). Prolonged inotropic support was defined as major catecholamines administration for ≥ 72 hours. The presence of one or more of these occurrences was defined as combined unfavorable outcome.

Patients population

A total of 79 patients were included in the study. Demographic data and univentricular cardiac anomalies are summarized in the table 1 and 2. Previous modified B-T shunt was done in 33 patients (41.77%) while 31 patients (39.24%) had previous pulmonary artery banding. 21 patients (26.58%) required previous atrial septectomy. Previous bidirectional Glenn was performed in 66 patients (83.5%), while 13 patients (16.5%) had bidirectional Glenn anastomosis at the same time of Fontan. The type of Fontan operation used was extracardiac conduit in 93.7% (n=74) of patients and the remaining patients had intracardiac tunnel (n=5). Fenestration was needed only in 10 cases (12.7%). All cases were operated on cardiopulmonary bypass. Aortic cross clamp and cardioplegia were used in 35.4% of cases (n=28). Eleven patients needed AV valve repair (13.9%). Median intensive care unit stay was 3 days (IQR: 2-4 days). Median hospital stay was 18 days (IQR: 13-25 days). There was no hospital mortality although 2 patients had Fontan take down due to failure and high pressure in the circuit. Post operative data are shown in table 3.

Statistical Analysis:

All continuous parameters were given as median and inter quartile range (IQR). Categorical data were summarized as frequencies and percentages. Univariable analysis using logistic regression was used to identify risk factors for prolonged hospital stay, prolonged pleural drainage duration, prolonged inotropic support and combined unfavourable outcome. The significant variables associated with combined unfavourable outcome were used to construct the multivariable logistic regression. P-value was considered significant when < 0.05. Data analyses were performed with Stata Statistical Software (Release 12; StataCorp 2011College Station. TX: StataCorp LP).

(3) Results

<u>Unfavourable postoperative outcome</u>

The statistical analysis on unfavorable early postoperative course was performed taking in consideration 28 variables.

1- Prolonged hospital stay, defined as hospital stay more than 25 days after Fontan completion.

2- Prolonged pleural effusion, defined as longer than 14 days.

3- Prolonged inotropic support, defined as catecholamine administration to maintain circulation for ≥ 72 hours.

<u>A- Prolonged hospital stay:</u>

Prolonged hospital stay > 25 days was found in 19 patients (24.05%). Univariable analysis for associated risk factors was done and shown in table 4. Significant risk factors correlated with prolonged hospital stay were low preoperative O_2 saturation (p 0.007), Fontan fenestration (p 0.009) and plasma transfusion in postoperative day 0 (p 0.030).

<u>B- Prolonged pleural effusion:</u>

Prolonged pleural effusion ≥ 14 days was found in 19 patients (24.05%). Univariable analysis for associated risk factors was done and showed that no significant risk factors were detected. Eleven patients (13.9%) required placement of additional chest tube for re-accumulation of pleural effusion after removal of previous chest tubes.

C- Prolonged inotropic support:

Prolonged inotropic support $\geq$ 72 hours was found in 28 patients (35.44%). Univariable analysis for associated risk factors was done and showed that significant risk factors were cardiopulmonary bypass time (P-value 0.003), fenestration (P-value 0.023), plasma transfusion in postoperative day 0 (P-value 0.028) and non staged Fontan with concomitant bidirectional Glenn at the same intervention (P-value 0.039) as shown in table 5.

D- Combined unfavorable outcome:

After studying combined outcome regarding the 3 variables we have selected for unfavorable outcome, we found that 33 patients (41.77%) lie in this category. Univariable and multivariable analyses by logistic regression were done for risk factors associated with unfavorable outcome and significant risk factors are shown in tables 6 and 7. In univariable analysis, risk factors were fenestration (P-value 0.019), long cardiopulmonary bypass time (P-value 0.026), low preoperative O_2 saturation (P-value 0.027) and plasma transfusion (P-value 0.036). In multivariable analysis, cardiopulmonary bypass time (P-value 0.168) and plasma transfusion (P-value 0.081) lost their significance, while significant risk factors were fenestration (P-value 0.030) with some trends towards low preoperative O_2 saturation (P-value 0.056).

(4) Discussion:

This study reviews 14 years experience of Fontan operation at IRCCS Policlinico San Donato (Italy) and evaluates the early outcome and the risk factors for postoperative unfavourable outcomes.

Regarding prolonged hospital stay after Fontan operation, Sasaki et al. [6] defined prolonged length of stay as hospital stay greater than 75 percentile after surgery which was defined greater than or equal to 15 days. Independent risk factors for prolonged length of stay included high hemoglobin level (odds ratio, 1.29; $p = 0.003$), high mean pulmonary artery pressure (odds ratio, 1.14; $p = 0.037$), low aortic saturation (odds ratio, 0.92; $p = 0.008$) and fenestration (odds ratio, 2.4; $p = 0.021$). Other previous studies focusing on prolonged hospital stay reported higher PAP, decreasing systemic oxygen saturation, old age and the diagnosis of HLHS as risk factors. [7, 8, 9]

In our study, prolonged hospital stay was found in 19 patients (24.05%). Significant risk factors were fenestration (P-value 0.009), low preoperative O_2 saturation (P-value 0.007) and plasma transfusion (P-value 0.030).

Our finding that the presence of a fenestration is associated with increased length of stay and postoperative complications is in contrast to most prior reports, and deserves mention. In many prior reports, fenestration has been associated with better outcomes [10, 11], including a decreased risk of death, decreased pleural effusion duration and less hospital stay. In particular, Lemler et al. [12] performed the prospective randomized trial to investigate the clinical utility of fenestration in patients with standard preoperative risk profiles for 49 consecutive Fontan operations. They concluded that baffle fenestration improves short term outcome in standard-risk patients by decreasing pleural drainage, hospital stay, and need for additional postoperative procedures. In our series, where fenestration was used in a particular subgroup of high risk patients, the association of prolonged length of stay and more complications is consistent with their high risk nature, rather than the presence of the fenestration per se. The same happened with plasma transfusion which was usually associated with low cardiac output state early in ICU and those patients represent more complex cases who needed more time for optimization of the cardiac output. It's recommended to perform Fontan completion early before deterioration of O_2 saturation because in our series it is found that low preoperative O_2 saturation is a risk factor for prolonged hospitalization.

Regarding pleural effusion, median drainage days was 8 days (IQR: 6-13 days). Pleural effusions after the Fontan operation contribute significantly to morbidity and prolonged hospitalization. Prolonged pleural effusion $\geq$ 14 days was found in 19 patients (24.05%) and no significant associated risk factors were detected. Gupta et al. [13] studied risk factors for persistent pleural effusion after extracardiac Fontan and stated that 37% had pleural drainage lasting > 14 days and significant risk factors were lower preoperative oxygen saturation (P-value, 0.011) and the presence of postoperative infections (P-value, 0.003). Fu et al. [14] reported that 38.9% of patients had pleural effusion for more than 15 days and multivariate analysis results showed that non-fenestration, low preoperative oxygen saturation, and postoperative infections were independent risk factors or prolonged pleural effusion. Fenestration of the Fontan baffle has been reported to significantly reduce the duration of pleural effusions in several reports. [11, 12]

In our experience we do not routinely perform fenestration of the extracardiac baffle. This procedure is reserved for patients with high risk hemodynamics and increased pulmonary pressure detected by increased CVP. In our study, the presence of fenestration was not found to significantly affect persistent pleural effusions.

In the study published by Ovroutski et al [15], prolonged inotropic support > 72 hours was found in 21,4 % of patients following Fontan completion demonstrating that heterotaxia, the presence of a systemic right ventricle, low preoperative arterial oxygen saturation and the use of cardioplegia were significant risk factors (P-value < 0.05).

In our series, prolonged inotropic support > 48 hours was found in 28 patients (35.44%). Significant risk factors were cardiopulmonary bypass time (P-value 0.003), fenestration (P-value 0.023), plasma transfusion (P-value 0.028) and non staged Fontan with concomitant bidirectional Glenn at the same intervention (P-value 0.039). Although both long cardiopulmonary bypass time and non staged Fontan are risk factors similar to those reported in the Literature, fenestration as a risk factor seems to be peculiar of our experience. The association of fenestration with prolonged inotropic support, prolonged hospital stay and combined unfavorable outcome is explained by patient selection and the indication of this procedure only in high risk cases.

Limitations:

The main limitation of the study is its relatively small number of patients, its retrospective nature and being a single center study. To detect more risk factors of unfavourable early outcome following Fontan completion and to ameliorate the postoperative course, a multicenter study with standard selection criteria may be needed in the future to refine statistical analysis outcomes and help in avoiding or reducing the risk of unfavourable early outcome after Fontan completion.

(5) Conclusion:

Unfavourable early outcome with prolonged hospital stay remains a frequent issue following Fontan completion. Risk factors include low preoperative O_2 saturation, prolonged cardiopulmonary bypass time, Fontan fenestration, Plasma transfusion and non staged Fontan.

Fontan staging, minimizing cardiopulmonary bypass time duration, optimizing low cardiac output treatment and early Fontan completion before deterioration of arterial O_2 saturation must be performed in order to improve the results in terms of complicated course with prolonged length of stay.

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Conflict of interest:

None.

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Tables:

Table 1: Demographic and preoperative data:

Variable	Mean	SD	Median	IQR	Min.	Max.
Age	9.66	6.29	7.3	5.6 - 11.5	2.88	33.9
Weight	28.47	16.03	21	17 - 37	12	84
Height	126.32	23.02	125	108 - 143	91	183
BSA	0.98	0.36	0.88	0.71 – 1.23	0.56	2.07
E F %	70.2	6.57	70	70 – 75	50	80
PAP mean	12.4	3.56	13	10 – 15	4	20
Creatinin preop	0.51	0.17	0.5	0.4 – 0.6	0.2	1.13
Ht. preop.	49.32	6.03	48.6	45 - 53.3	38	74
Bilirubin preop.	0.88	0.56	0.71	0.5 – 1.05	0.21	3.4
Glenn-Fontan interval yrs	6.45	4.72	5	3.5 – 8	1	27

BSA= Body surface area, EF%= Ejection fraction, PAP mean= mean pulmonary artery pressure, Ht=hematocrit

Table 2: Diagnosis

Diagnosis	N	Percentage(%)
Tricuspid atresia	20	25.32%
DORV	15	18.99%
DILV	10	12.66%
HLHS	8	10.13%
AVSD	5	6.33%
Isomerism	4	5.06%
Pulmonary atresia	3	3.80%
TGA	6	7.59%
Univentricular heart	5	6.33%
CC-TGA	3	3.80%
Total	79	100%

Table (1): List of diagnosis
DORV= double outlet right ventricle , DILV= double inlet left ventricle , HLHS= hypoplastic left heart syndrome , AVSD= atrio ventricular septal defect , TGA= transposition of great arteries , CC-TGA= congenitally corrected transposition of great arteries.

Table 3: Post operative features:

Variable	Mean	±SD	Median	IQR	Min	Max
Heart rate	115.5	18.05	118	103 – 130	70	148
MAP	68.6	15.20	69	56 – 79	34	103
CVP	15.2	3.1	15	13 – 18	7	23
Hct	37.4	6.55	37	33 – 41	25	71
MV (hrs)	23.5	69.6	11	7 – 16	1	560
Drainage Days	10.66	6.04	8	6 – 13	3	27
ICU Stay	3.7	3.98	3	2 – 4	1	30
Hospital Stay	21.11	11.55	18	13 – 25	8	64

MAP= mean arterial pressure, CVP= central venous pressure, Hct= hematocrit%, MV= mechanical ventilation .

Table 4: Univariable analysis of risk factors of prolonged hospital stay

Variables	Odds Ratio	Standard error	Z	P-value	95% Confidence interval
Age	0.96	0.05	- 0.80	0.424	0.87 – 1.06
Weight	1.006	0.016	0.38	0.704	0.97 – 1.04
Height	1	0.012	0.01	0.991	0.978 – 1.023
BSA	1.23	0.897	0.28	0.780	0.29 – 5.14
Pap mean	1.01	0.75	0.11	0.909	0.87 – 1.167
Preop. O2 saturation	0.896	0.04	- 2.70	0.007	0.83 – 0.97
Creatinine Preop	0.36	0.605	- 0.61	0.543	0.014 – 9.58
Hct	0.995	0.044	- 0.12	0.901	0.912 – 1.08
Bilirubin	0.56	0.33	- 0.98	0.33	0.179 – 1.78
Diagnosis	1.187	0.108	1.89	0.059	0.99 – 1.42
mB-T shunt	0.76	0.41	- 0.50	0.618	0.26 – 2.21
PA banding	1.55	0.83	0.83	0.407	0.55 – 4.41
BD Glenn	1.91	1.56	0.79	0.430	0.38 – 9.49
Avv regurge	0.96	0.197	- 0.20	0.840	0.64 – 1.43
Antegrade flow	1.16	0.66	0.27	0.784	0.39 – 3.52
Preop. arrhythmia	1.06	1.25	0.05	0.964	0.103 – 10.79
Extracardiac	1.29	1.48	0.22	0.827	0.134 – 12.26
Fenestration	6.46	4.62	2.61	0.009	1.59 – 26.25
Bypass time	1.005	0.006	0.78	0.438	0.99 – 1.02
Low Hct	0.95	0.056	- 0.94	0.345	0.84 – 1.06
Low temp.	1.03	0.14	0.19	0.852	0.79 – 1.34
MAP	1	0.017	0.05	0.959	0.97 – 1.04
CVP	1.014	0.87	0.16	0.873	0.86 – 1.199
Hct	1	0.039	0.24	0.807	0.93 – 1.09
Transfusion	6	6.42	1.67	0.094	0.74 – 48.84
Blood	2.68	1.66	1.59	0.112	0.79 – 9.04
Plasma	4.36	2.97	2.16	0.030	1.15 – 16.56
Platelets	0.36	0.396	- 0.93	0.352	0.042 – 3.09

BSA = body surface area, pap= pulmonary artery pressure, MAP= mean arterial pressure, CVP= central venous pressure.

Table 5: Significant risk factors associated with prolonged inotropic support:

Variables	Odds Ratio	Standard error	Z	P-value	95 % Confidence interval
BD Glenn	0.27	0.17	- 2.07	0.039	0.08 – 0.93
Fenestration	5.33	3.94	2.27	0.023	1.26 – 22.66
Bypass time	1.02	0.007	3	0.003	1.007 – 1.04
Plasma	3.26	1.76	2.19	0.028	1.13 – 9.38

Table 6: Significant risk factors associated with combined unfavorable outcome after univariable analysis:

Variables	Odds Ratio	Standard error	Z	P-value	95 % Confidence interval
Fenestration	7.04	5.84	2.35	0.019	1.39 – 35.77
Bypass time	1.01	0.006	2.23	0.026	1.002 – 1.03
Plasma	2.86	1.44	2.10	0.036	1.07 – 7.66
O2 sat. %	0.92	0.35	- 2.21	0.027	0.85 – 0.99

Table 7: Multivariable analysis for significant risk factors associated with unfavorable outcome:

Variables	Odds Ratio	Standard error	Z	P-value	95 % Confidence interval
fenestration	7.35	6.53	2.14	0.025	1.29 – 41.95
Bypass time	1.01	0.007	1.38	0.168	0.996 – 1.02
Plasma	2.67	1.50	1.74	0.081	0.89 – 8.06
O2 sat. %	0.93	0.04	- 1.91	0.056	0.86 – 1.002