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UNIVENTRICULAR HEART SURGERIES: ANALYSIS AND OPTIMIZATION

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Biomedical Sciences, Medicine (06B)

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VILNIAUS UNIVERSITETAS

LAURYNAS BEZUŠKA

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Abbreviations

ABG – arterial blood gas

BP – blood pressure

CICU – cardiac intensive care unit

CO2 –carbon dioxide

CVP – central venous pressure

EF – ejection fraction

ePTFE – expanded polytetrafluoroethylene

$ETCO_2$ – end tital CO_2

FP – Fontan procedure

FV – femoral vein

HLHS – hypoplastic left heart syndrome

HR – heart rate

IJV – internal jugular vein

IQR – interquartile range

IVC – inferior vena cava

LV – left ventricle

NO – nitric oxide

PAP – pulmonary artery pressure

PVR – pulmonary vascular resistance

RPM – revolutions per minute

SD – standard deviation

SR – sinus rhythm

TCPC – total cavopulmonary connection

TTE – transthoracic echocardiography

VAD – ventricular assist device

VADC – VAD connection

VADD – VAD disconnection

VUH SK – Vilnius University Hospital Santaros Klinikos

1. INTRODUCTION

1.1. Relevance of the problem

Single ventricle is a rare, but complex heart defect. The implied prevalence of the defect is 16 to 80 cases per 100 000 live births [1]. One of the two ventricles can be smaller, altered or with an undeveloped valve. The natural course is usually unfavourable [2]. Even with palliative operations, historically the "best" three-year survival rate was 75% [3].

It is impossible surgically to form a normal circulation with a right ventricle pumping blood to the lungs and a left ventricle delivering blood to the rest of the body to a child who is born with a single ventricle. Such univentricular heart is nonseptable or lacking two well-developed ventricles. These patients undergo the creation of a single ventricle or Fontan circulation [4]. These procedures usually consist of three stages [5]. The final stage is Fontan surgery [6]. Fontan described this procedure for the first time back in 1971 [4]. Despite that, even nowadays authors are describing new modifications of the Fontan surgery or methods of the perioperative treatment in order to improve early and late mortality and morbidity results. These modifications include:

- Extracardiac Fontan [7] with or without fenestration [8] using cardiopulmonary bypass or without [9];
- Late closure of fenestration or leaving it opened [10];
- The usage of sildenafil, iloprost or nitric oxide (NO) gas [11].

Preoperative, operative, and postoperative monitoring of patients is improving as well [12]. New guidelines are introduced which suggest the administration of NO gas, sildenafil and iloprost [11]. The attitude regarding the timing of the Fontan operation is changing as well. Nowadays, Fontan operations are carried out in increasingly younger patients unlike previous times [13]. Earlier procedures can avoid formation of venovenous or aortopulmonary collaterals, which have a negative impact on both the early and the late postoperative results [14]. The ongoing debate is regarding the most favourable time to perform the Fontan operation [15]. As early results are improving, the attention is shifting towards late results and the quality of life [16]. The question is what speciality doctors should monitor these patients. Special multidisciplinary centres are

introduced for long follow-up [17]. Despite considerable progress, patients with single ventricle circulation have worse quality of life than the general population [18]. Eventually patients start to suffer from specific late complications:

- Plastic bronchitis,
- Protein-losing enteropathy,
- Arrhythmia,
- Liver failure,
- Thromboembolism,
- Lymphatic system failure,
- Deficits in bone density and structure,
- Decreased muscle mass,
- Fountain circulatory failure [19].

Thus, the novelty and relevance of the dissertation is to analyse Fontan operations, which were carried out in Vilnius University Hospital Santaros Klinikos (VUL SK). The collected data will be used to create Fontan patients database, which is very important for long-term, usually life-long monitoring of these patients. According to the study results, recommendations will be suggested on how to optimize treatment and improve patients' outcomes and quality of life. Almost 100 Fontan surgeries were performed at the VUH SK Centre of Heart and Chest Surgery. That is a sufficient amount for data analysis.

1.2. The aim of the study

To analyse single ventricle circulation forming Fontan-type operations performed at the VUH SK Centre of Heart and Chest Surgery. Furthermore, the study aims to evaluate Fontan modifications and effectiveness comparing early and late results, statistically significant differences between different groups of Fontan patients, frequency of complications, age at the Fontan operations and the duration of the drainage from pleural cavities after procedures.

1.3. Objectives of the study

1. To compare the early and late surgical results of different Fontan modifications. To determine the estimated survival rate of these groups.

2. To evaluate the results of Fontan operations performed in children younger than 3 years of age compared to Fontan operations performed in older patients.

3. To illuminate the effectiveness of the ventricular assist devices in the complicated postoperative course.

4. To evaluate the effectiveness of anticoagulation and the prevalence of thrombosis in the postoperative period. To recommend antithrombotic therapy guidelines.

5. To provide guidance on how to improve the course, outcome, and quality of life after Fontan completion surgeries.

1.4. Principal statements for defence

1. The results of Fontan operations while using extracardiac expanded polytetrafluoroethylene (ePTFE) conduits are good and consistent with the results of the best cardiac centres.

2. Fontan completions for children under 3 years of age are safe. Early and late outcomes are good and consistent with the results of operations performed to older patients.

3. The duration of drainage from pleural cavities is significantly shorter in patients undergoing Fontan completion under 3 years of age.

1.5. Scientific novelty of the study

1. *PubMed*, *Cochrane*, and *Web of Science* databases contain only a few publications that publish late Fontan results with a tracking period of over 30 years. Most articles describe the results of shorter-term studies. This dissertation presents the long-term follow-up results at the VUH SK.

2. Different centres do not share the same opinion about the optimal age of the patients to perform Fontan operations. Some of the patients undergo Fontan completion younger than 3 years of age at the VUH SK Centre of Heart and Chest Surgery. Furthermore, the results showed that the outcome of the operations at the younger age are good. The drainage from the pleural cavities is statistically significantly shorter if patients undergo Fontan completion earlier.

3. There are currently no generally accepted algorithms for the use of mechanical circulatory assist devices in the development of acute severe cardiac failure after Fontan completion. A successful cardiac support with a ventricular assist device (Levitronix PediVAS) in our centre could be a good solution for both short-term cardiac failure treatment and prolonged maintenance of the circulation in anticipation of cardiac transplantation.

1.6 Practical importance of the study

The patients who underwent Fontan completion at the VUH SK Centre of Heart and Chest Surgery within the 31-year period (1985-2015) were evaluated for their late results. This is the first such study in the Baltic States. The study showed Fontan operations using an extracardiac conduit to be good. The results are similar to the best cardiac centres. The study concluded the Fontan procedures performed at the earlier age are safe and late follow-up results are encouraging. The chest drains are removed significantly earlier if the surgery is performed at the younger age. This is particularly important for patients with worsening cyanosis, decreasing physical activity and failure to thrive. An earlier operation could improve physical activity and circulation.

The recommendations are presented based on the data collected and summarized in the study. They specify how to improve treatment and quality of life in patients after Fontan surgery. This is relevant in the scientific sense and for the patients themselves.

2. METHODS

2.1. Patient population

The study has been conducted at the VUL SK Centre of Heart and Chest Surgery during the period 2012 – 2016. The local Ethics Committee approved the study. This is an observational, non-randomized, retrospective and prospective monocentric study. Control group was not possible in this study because the outcome of the non-operated children with this pathology is unfavourable. The study included all functional single ventricle patients who underwent the final phase of Fontan completion. A written consent to participate in the study has been obtained from all prospective study participants or their parents (carers). Single ventricle surgeries are performed only at VUH SK in Lithuania. Data was collected from VUH SK electronic information system ELI and medical documentation such as paper medical records, operation notes, anaesthesia protocols and outpatient cards. All patients who participated in the study were monitored and examined according to the procedures established by VUH SK.

Patients in the study had had Fontan completion accomplished from January 1, 1985 to December 31, 2015. There were 83 patients in total (39 females and 44 males). All patients were divided into four groups according to the surgical procedure. Twenty-one patients had atriopulmonary Fontan (Group I) between 1985 and 1998. Four children received an intra-atrial lateral tunnel (Group II) in 1993 – 2000. Six patients underwent extracardiac total cavopulmonary connection (TCPC) with an aortic homograft (Group III) in 1996 – 2005. The remaining 52 children (Group IV) who operated between 2000 and 2015 had extra-cardiac TCPC with expanded polytetrafluoroethylene (PTFE) conduit (Table 1). This artificial denture is better known by the name GORE-TEX® (W. L. Gore & Associates, Flagstaff, AZ). Table 1 presents the distribution of the patients according to the type of surgery and the period of the modification.

Table 1. Distribution of the patients by the type of Fontan surgery and accomplishment year.

Fontan type	**Number of patients (% of total 83 patients)**	**Time period, years**
Atriopulmonary Fontan	21 (25)	1985–1998
TCPC with lateral tunnel	4 (5)	1993–2000
TCPC with extracardiac aortic homograft	6 (7)	1996–2005
TCPC with extracardiac expanded PTFE conduit	52 (63)	2000–2015

Morphologically dominant left ventricle was detected in 70 (84%, 70/83) patients. The most common initial diagnosis was tricuspid atresia (34%, 28/83). Common ventricle was found in 25 (30%, 25/83) patients. HLHS was confirmed in nine (11%, 9/83) patients. Pulmonary atresia with right ventricular hypoplasia was found in eight (10%, 8/83) patients. The rest 13 (16%, 13/83) patients had other types of single ventricle defects. Table 2 lists diagnoses and distribution of congenital heart diseases among four Fontan groups.

Table 2. List of diagnoses and distribution between Fontan groups.

Diagnosis	**Group I, n=21**	**Group II, n=4**	**Group III, n=6**	**Group IV, n=52**
Type of morphological ventricle (LV/RV)	20/1	3/1	5/1	42/10
Tricuspid valve atresia	4	1	4	19
Single ventricle	14	1	-	10
Hypoplastic left heart syndrome	-	1	-	8
Pulmonary artery atresia	2	1	-	5
Other	1	-	2	10

2.1.1. The main criteria for inclusion in the study

1. Patients with a single ventricle (left, right or without ventricular septum) whom is surgically impossible to create normal human circulation.

2. Patients who have had the surgical staged completion of the single ventricle circulation and the final one is Fontan surgery.

3. Only those patients included in the study who underwent surgeries at the VUH SK Centre of Heart and Chest Surgery.

2.1.2. Possible risks and harm to subjects

All patients included in the study received routine treatment. Therefore, the subjects were not at higher risk than any other patient who did not participate in the study. Information about the treatment and the examination performed is confidential and will only be provided to the treating physician in the normal way. Side effects were not recorded because the study was observational and did not affect the treatment.

2.2. Operation technique

The standard procedure has been to establish TCPC using ePTFE conduit with cardiopulmonary bypass at the VUH SK Centre of Heart and Chest Surgery. Median sternotomy is performed. Usually it is redo sternotomy due to previous initial surgical stages. The right atrium is completely mobilized from the pericardium preparing the space for the future conduit.

The ascending aorta and the superior and inferior caval veins are cannulated. The cardiopulmonary bypass is commenced at mild hypothermia (32-34°C) and the surgery is continued on beating heart. Cold blood cardioplegic arrest is used for short periods if intracardiac repair needed.

An 18 or 20 mm ePTFE conduit is used for creation of TCPC. The diameter of the conduit depends on the weight of the patient, anatomical cardiac arrangement and the size of inferior vena cava (IVC). The inferior wall of the right pulmonary artery is opened along its length. The incision is extended to the level of the main pulmonary artery and right pulmonary artery bifurcation. The conduit is fashioned slightly obliquely and anastomosed with a 6-0 or 5-0 running Prolene (Ethicon, Somerville, NJ) suture.

IVC is clamped at the junction with the atrium and divided by leaving a small atrium cuff on the vein. This cuff provides wider anastomosis and greater growth potential. The right atrium is closed. The conduit is cut in size and anastomosed to IVC stump with a continuous 4-0 or 5-0 running Prolene suture. If necessary, the fenestration is created between the conduit and the right atrium. The cardiopulmonary bypass is weaned off and drains are inserted into both pleural cavities and behind the sternum. The chest is closed in a standard manner. The patient is extubated as soon as possible in the theatre or on arrival to intensive care unit.

For the last 5 years, patients undergo modified ultrafiltration at the end of the surgery. Warfarin is commenced few days after the procedure. Anticoagulation treatment lasts 6 months after surgery. Aspirin replaces warfarin later if there are no thrombotic events.

2.3. Definitions

Operative mortality was defined as death occurring within 30 days of surgery or before hospital discharge. Overall mortality was counted as early mortality combined with late mortality at follow-up.

2.4. Statistical analysis

The statistical software SPSS 21.0 for Windows (SPSS Inc. Chicago, Illinois, USA) and Microsoft Office Excel 2013 were employed. A value of $p < 0.05$ was considered to be significant and $0.05 < p \leq 0.1$ was considered as a trend.

Histograms, rectangular diagrams and Shapiro-Wilk test ($p > 0.05$) were used to detect departures from normality of continuous variables ($p > 0.05$). Normally distributed quantitative data is expressed as mean ± standard deviation (SD). Quantitative continuous non-normal distributed variables are presented as median and interquartile ranges (IQR). The Mann-Whitney U test was employed to compare continuous variables.

Categorical variables were compared by using $\chi 2$ or Fisher exact test and are presented as numbers or percentages. The survival rate was evaluated using the Kaplan-Meier method. The groups were compared using the log rank test. Patients were

compared according to Fontan modifications (Groups I to IV) and the age at the procedure (Groups A and B). The overall survival rate of 1, 5, 10 and 15 years was evaluated between Groups I to IV. Patients were censored if follow-up was finished.

3. RESULTS

The average follow-up time was 7.9 ± 6.6 years. The median age for the Fontan completion was 4.5 (IQR: 3.1-7.6) years. Eight patients lost at follow-up. The first patient who survived until the late period underwent surgical procedure in 1989. The follow-up time is more than 26 years. The youngest patient undergoing Fontan surgery was 14 months old. This patient underwent TCPC with a 20 mm diameter extracardiac ePTFE conduit. The oldest patient had atriopulmonary Fontan at 26 years of age. Nineteen patients (37%, 19/52) underwent TCPC with extracardiac ePTFE conduit younger than 3 years of age. The main clinical criteria for the early operation were worsening cyanosis, diminishing physical activity and failure to thrive. The average weight was 15.6 ± 5 kg and the average height was 101 ± 16.4 cm. Preoperative mean pulmonary arterial pressure was 13.4 ± 3.4 mm Hg and pulmonary vascular resistance was 1.2 ± 0.6 WU*m^2. Forty free (52%, 43/83) patients received fenestration. The median length of stay in intensive care unit, intubation and chest drain stay time were 89.5 (IQR: 46.3-119) hours, 8 (IQR: 6-16) hours and 18 (IQR: 12- 28) days respectively. Nine (11%, 9/83) patients received Fontan completion as a primary operation. All others had initial staged procedures before Fontan completion.

Table 3 shows initial operations and their distribution among Fontan groups. The most common first-stage operation was a modified Blalock-Taussig shunt, which was performed on 25 (30%, 25/83) patients. Eighteen (22%, 18/83) children had pulmonary artery banding. Eleven (13%, 11/83) patients received central shunt and eight (10%, 8/83) patients had modified Norwood. Bidirectional Glenn was created as a second-stage procedure if needed. Twelve (14%, 12/83) children have this anastomosis formed as an initial palliative surgery. The last few year Fontan operation is performed only after the initial staged interventions in order to achieve a better outcome.

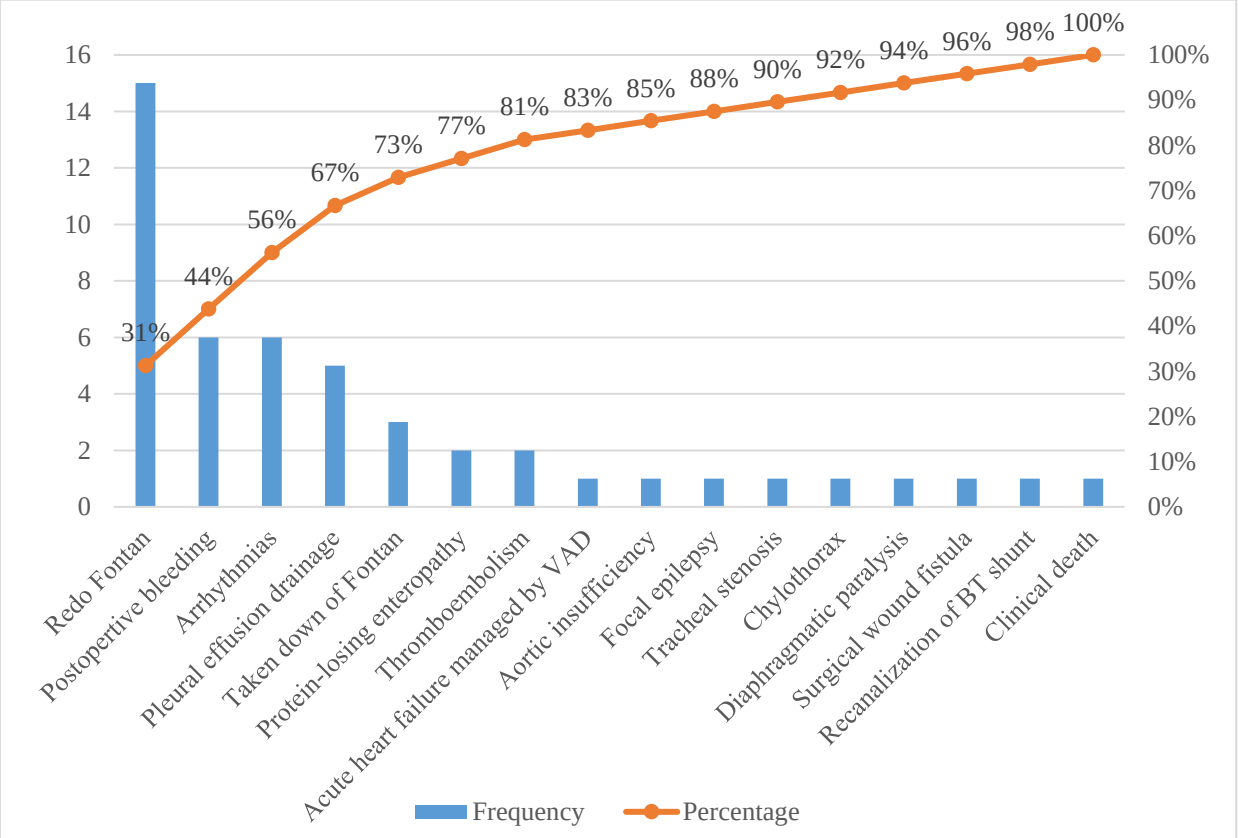
Table 3. Staged procedures at the initial palliation.

Procedure	Group I, n=21	Group II, n=4	Group III, n=6	Group IV, n=52
Modified Norwood	-	-	-	8
Modified Blalock–Taussig shunt	11	1	3	10
Central shunt	1	1	-	9
Pulmonary artery banding	1	1	2	14
Initial Glenn	-	1	-	11
Fontan procedure	8	-	1	-

3.1. Morbidity

Early complications were severe bleeding (6), pleural effusion drainage (5), taken down of Fontan circulation (3), chylothorax (1), diaphragmatic paralysis (1), focal epilepsy (1), acute heart failure managed by left heart bypass (1) and surgical wound fistula (1). Late complications manifested as arrhythmias (6), protein-losing enteropathy (2), thromboembolism (2), aortic insufficiency managed by valvuloplasty (1), tracheal stenosis (1), recanalization of Blalock-Taussig shunt (1), and clinical death followed by a successfully resuscitation (1). Figure 1 shows Fontan complications as a Pareto diagram.

Figure 1. Pareto diagram showing distribution of complications after Fontan surgery.



3.1.1. Redo Fontan procedures

Fourteen (17%, 14/83) patients underwent redo Fontan procedures (Table 4). Two (14%, 2/14) patients died in the early postoperative period. The highest number of redo Fontan procedures was in Group I. Nine surgical interventions were performed in eight (38%, 8/21) patients. The main indications were dilated right atrium and arrhythmias. Patients had eight Fontan conversions in this group. One patient had redo Fontan twice. This patient the first time had atriopulmonary Fontan converted to TCPC with a lateral tunnel using aortic homograft. The second time the lateral tunnel Fontan was redone for extracardiac TCPC with ePTFE conduit. Three others received extracardiac TCPC with ePTFE conduit and the other three had TCPC with lateral tunnel. The last patient had a taken down of Fontan circulation to hemi-Fontan due to severe Fontan circulatory failure. One year later, this patient received a redo atriopulmonary Fontan. No patient has been re-operated in the lateral tunnel group. Three patients from group III needed aortic homografts to be replaced with an extracardiac ePTFE conduit due to developed stenosis. Three (6%, 3/52) patients had their narrowed ePTFE conduits refashioned with larger 22 mm GORE-TEX® tubes in group IV.

Table 4. Redo Fontan procedures.

Redo procedure / **Procedure**	**TCPC with ePTFE tube, n**	**TCPC, lateral tunnel, n**	**Atriopulmonary Fontan, n**
Atriopulmonary Fontan, n=21	4	4	1
TCPC with lateral tunnel, n=4	0	0	0
TCPC with extracardiac aortic homograft, n=6	3	0	0
TCPC with extracardiac ePTFE conduit, n=49	3	0	0

3.2. Mortality

Seven (8%, 7/83) patients died in the early postoperative period and nine (12%, 9/76) died later. Most of the deaths (63%, 10/16) have occurred in Group I. The Kaplan-Meier curves show a marked improvement in the survival rate between different Fontan

groups (Figure 2). A cumulative survival rate was 42% in Group I, 50% in Group II, 83% in Group III and 94% in Group IV. Table 5 presents a cumulative survival rate of 1, 5, 10, and 15 years based on the Kaplan-Meier method. The best results were obtained in Group IV ($\chi 2$ - 15,989, p = 0.001). The last mortality was recorded in 2010. No patient has died during the last 5 years.

Table 5. The total estimated survival of 1, 5, 10 and 15 years based on the Kaplan-Meier method.

Fontan Group	**Total estimated survival (% ± SD)**			
	1-year	**5-year**	**10-year**	**15-year**
I	66 ± 11 %	60 ± 12 %	54 ± 12 %	42 ± 12 %
II	75 ± 21 %	50 ± 25 %	50 ± 25 %	50 ± 25 %
III	83 ± 15 %	83 ± 15 %	83 ± 15 %	83 ± 15 %
IV	96 ± 3 %	94 ± 3 %	94 ± 3 %	94 ± 3 %

Five early deaths in Group I were associated with cardiac failure and multiple organ dysfunction syndrome. In addition, five patients died in the late period in Group I. One child died one and a half years after initial failed Fontan that needed to be converted to Glenn. This patient died in early postoperative period after redo Fontan due to acute heart failure. Another patient died 11 years after the Fontan procedure secondary to right atrial thrombosis. The third child died 12 years later due to unintentional drowning while swimming in a lake. The other two patients died late due to unconfirmed reasons.

There was one early death due to multiple organ failure and one late death due to cardiac arrhythmia in Group II. The only one patient died late in Group III for unknown reason. Three children out of 49 died in Group IV. One early death occurred on the second postoperative day due to sudden cardiac arrest and unsuccessful resuscitation. The second early mortality case appeared 6 weeks post-Fontan procedure because of progressing heart failure and severe draining. The predisposition of the late death was severe protein-losing enteropathy. The child died due to acute heart and multiple organ failure two days later after Redo TCPC. Table 6 presents the distribution of mortality among different groups of patients.

Figure 2. Kaplan-Meier survival in different types of Fontan procedures. The plot is adjusted by power. Group I – Atriopulmonary Fontan. Group II – Lateral Tunnel. Group III –TCPC with aortic homograft. Group IV – TCPC with ePTFE conduit. ($\chi 2$ - 15,989, p = 0.001)

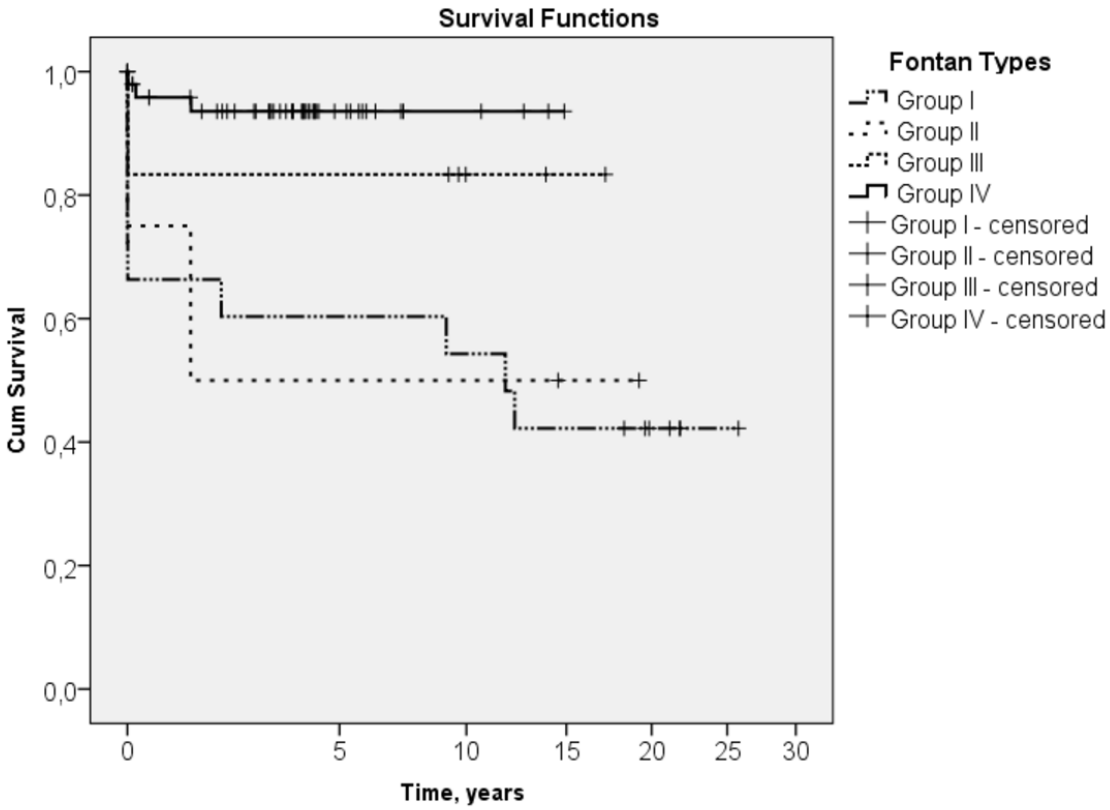


Table 6. Distribution of mortality among different Fontan groups.

Procedure	**Group**	**Number of patients**	**Mortality, n**		
			Early	**Late**	**Total**
Atriopulmonary Fontan	I	21	5 (24 %)	5 (31 %)	10 (48 %)
TCPC with lateral tunnel	II	4	1 (25 %)	1 (33 %)	2 (50 %)
TCPC with extra-cardiac Ao homograft	III	6	0 (0 %)	1 (17 %)	1 (17 %)
TCPC with extra-cardiac ePTFE conduit	IV	52	2 (4 %)	1 (2 %)	3 (6 %)
TOTAL	-	83	7 (9 %)	9 (12 %)	16 (19 %)

3.3. Results of Fontan operations in patients under 3 years of age

One of the main goals of the study was to determine if TCPC with extracardiac ePTFE conduit is safe for children under 3 years of age. Forty-five patients (25 boys and 20 girls) were included into the study. All these patients underwent an extracardiac Fontan operation with an iPTFE conduit in 2000-2013. Patients were divided into two groups depending on the age at Fontan procedure. Group A consisted of 15 children who had Fontan completion younger than 3 years of age. Other 30 patients (Group B) underwent the operation while being older. The time of Fontan completion was decided based on clinical symptoms as worsening cyanosis, decreasing physical activity and failure to thrive. The age range in Group A was from 14 months to 2.9 years. Patients in Group B were from 3.1 to 12.6 years old. The minimum weight and height was 9 kg and 74 cm in Group A compare with 11.2 kg and 90 cm in Group B. Oppositely, the maximum weight and height was 15.5 kg and 96 cm in Group A versus 35 kg and 146 cm in Group B. Preoperative median ventricular function was 60 % in both groups. Table 7 presents distribution of congenital heart defects and statistical significance between the two groups.

Table 7. List of diagnoses and association.

Diagnosis	**Group A n=15**	**Group B n=30**	**p value** Fisher's exact test
Type of morphological ventricle (LV/RV)	12/3	25/5	0.542
Hypoplastic left heart syndrome	3	3	0.384
Tricuspid valve atresia	3	13	0.189
Single ventricle	4	6	0.710
Pulmonary artery atresia	1	3	0.593
Other	4	4	0.410

Median follow-up time was 2.9 (IQR: 2 – 4.4) years. One child in Group A and one in Group B were lost at follow-up. Demographic related parameters, as age, weight, and height differed statistically significantly between two groups (Table 8). The median intensive care unit and hospital stay were not significant between two groups. Preoperative and postoperative ventricular ejection fraction was similar in both groups.

The duration of pleural effusion drainage was significantly lower in Group A than in Group B with p = 0.014.

The most common initial staged procedure was pulmonary artery banding (31%, 14/45). The central shunt was less common (18%, 8/45). This operation was performed only for patients in Group B and it was the only statistically distinct procedure between the two groups. Seven (16%, 7/45) children received modified Blalock-Taussig shunt and five (11%, 5/45) had modified Norwood. Table 9 shows staged procedures at the initial palliation in Group A and B. All patients from both groups had previously undergone bidirectional Glenn anastomosis as a staged approach before TCPC.

Table 8. Association between variables and age groups (group A: < 3 years versus group B: ≥ 3 years) at Fontan completion.

Variable	**Median**		**IQR**		**p value** Mann-Whitney U test
	Group A	**Group B**	**Group A**	**Group B**	
Demographic related variables					
Age, years	2.1	4.5	1.7 – 2.6	3.9 – 7.7	<0.001
Weight, kg	12.2	16.5	11 – 13.2	13.2 – 19	<0.001
Height, cm	88	108	83 – 91	95 – 115	<0.001
Disease related variables					
Preoperative Ventricular EF, %	60	60	50-60	54-66	0.318
Postoperative Ventricular EF, %	55	59	50-61	50-60	0.421
Preoperative Glenn pressure, mm Hg	14	12	12-16	10-14	0.064
Preoperative PVR, Wood units	1	1	0.9 – 1.3	1 – 1.4	0.371
Procedure related variables					
Conduit size, mm	20	20	20	20-22	0.056
Intubation, h	6	7	6-20	5-14	0.853
CICU stay, h	90	65	46-140	45-115	0.322
Hospital stay, d	21	29	16-33	21-39	0.057
Chest drain stay, d	12	22	7-22	16-33	0.014

Table 9. Staged procedure at the initial palliation.

Procedure	**Group A** **n=15**	**Group B** **n=30**	**p value** Fisher's exact test
Modified Norwood	3	2	0.315
Blalock-Taussig shunt	3	4	0.670
Central shunt	0	8	0.038
Pulmonary artery banding	4	10	0.743
Initial Glenn	5	6	0.464

Fontan fenestration was created for 11 patients (73%) in Group A and for 21 patients (70 %) in Group B. Median size of the ePTFE conduit was 20 mm in both groups. Mortality, gender and presence of fenestration were not significant as categorical variables (Table 10).

Table 10. Association between categorical variables and age groups at Fontan completion.

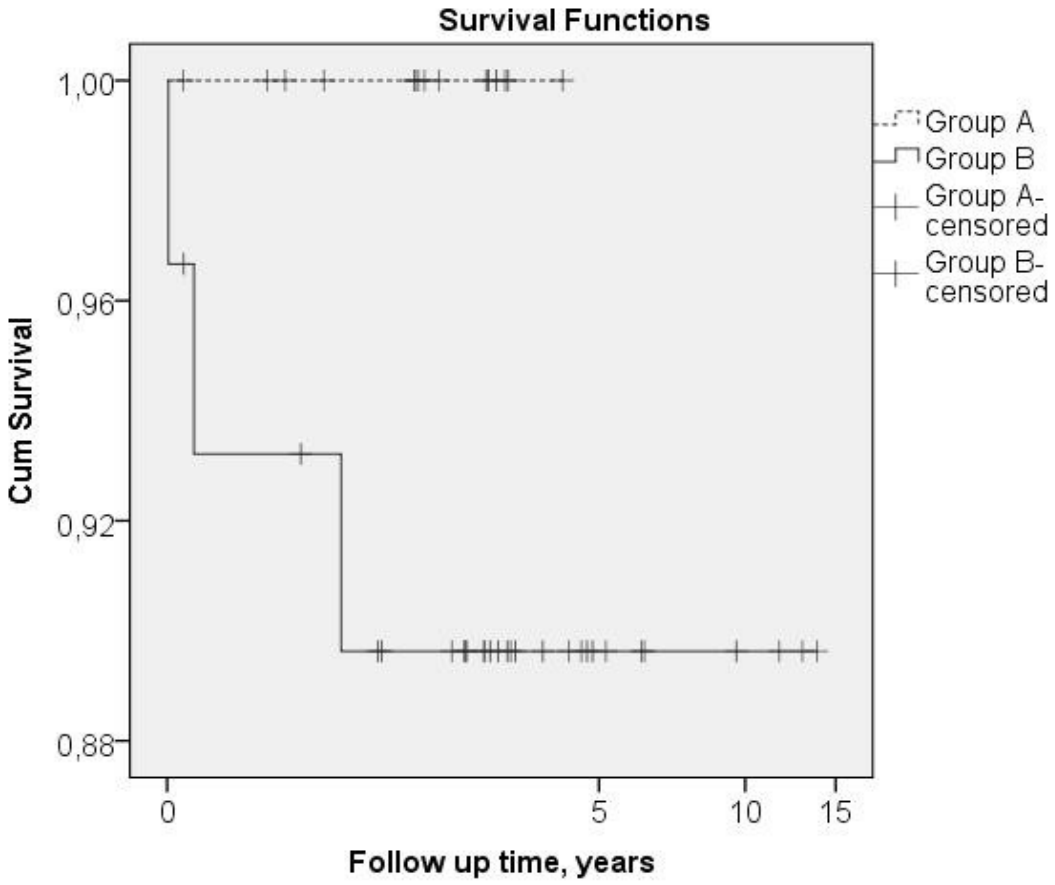
Variable	**p value** Fisher's exact test
Mortality	0.286
Gender	0.540
Fenestration	0.553

All Fontan candidates underwent cardiac catheterization before surgery. Table 8 displays data for Glenn pressures and pulmonary vascular resistance. In accordance with our institutional policy, cardiac catheterization after Fontan surgery was performed only due to a clinical deterioration of a patient. For this reason majority of patients did not have a catheter procedure after TCPC.

Two hospital deaths and one late death were recorded. All of these patients were from group B. The causes of these deaths are described in section 3.2. The Kaplan-Meier method shows the survival differences between the two groups of patients (Figure 3). Mortality did not statistically differ between Group A and B ($\chi 2$ -1.422, p = 0.233).

These data suggest that surgery at a younger age is safe and the late outcomes are similar to the older patients group.

Figure 3. Kaplan-Meier survival functions after Fontan surgery for patients in Group A and Group B. The plot is created and adjusted by power.



3.4. Successful acute heart failure treatment with VAD

A three-year-old male underwent Fontan procedure as TCPC with extracardiac fenestrated iPTFE conduit. His initial diagnosis was tricuspid atresia with hypoplastic right ventricle. The second postoperative day the patient developed a severe acute heart failure. A multisystem organ failure started to manifest. Transthoracic echocardiography (TTE) revealed a single ventricle with an ejection fraction of 30%. Mainstay treatment with maximal inotropic support as well peritoneal dialysis was ineffective.

Levitronix PediVAS (Levitronix LLC, Waltham, MA) was chosen as a ventricular assist device. ECMO was refused as we were considering the possibility of long-term heart failure. Levitronix can provide support for 30 days and longer. On the other hand, ECMO for long-term is not recommended [20]. Levitronix was chosen as a bridge to healing or heart transplantation.

Single ventricle (left heart bypass) support with the PediVAS device was initiated through redo median sternotomy by placing a 12-French Medtronic DLP arterial cannula to the ascending aorta and bent angle wire-reinforced 18-French Terumo® venous cannula to the dome of the common atrium. These cannulae were connected with air-free Levitronix tubes. The cannulas were tunnelled through the skin and the chest was closed. An oxygenator was not used. On the initial phase the speed of PediVAS was chosen as a full cardiopulmonary flow speed in the normothermic condition at 1.7 L/min and 4300 rpm. Flows were maintained between 0.3 and 1.7 L/min at 2350-4400 rpm. Table 11 presents dynamics of PediVAS, arterial blood gas and saturation parameters as well dosage of inotropes.

Intravenous unfractionated heparin was administered in subtherapeutic doses due to increased bleeding. The status of the patient was gradually improving. Blood tests could demonstrate the progress as well (Table 12). After 4 days of circulatory support, weaning trials revealed significant recovery of the heart and the Levitronix support system was successfully explanted. VAD was weaned off after the patient being hemodynamically stable for 2 hours on very low device flow (0,3 l/min). TTE showed improved ventricular function with an ejection fraction of 40%. Gradually the child recovered and he was discharge home. One year later, the boy was doing well and ventricular ejection fraction was measured as 55% by TTE.

Table 11. Dynamics of PediVAS parameters, dosage of inotropes, arterial blood gas and saturation values in acute phase.

Time / **Parameters**	**Just after FP**	**24h after FP**	**48h after FP/ just after VADC**	**24h post VADC**	**48h post VADC**	**72h after VADC**	**93h(just before VADD)**	**24h after VADD**	**48h after VADD**
VAD, l/min.	-	-	1,7	1,7	1,37	1,32	0,3	-	-
RPM	-	-	4300	4350	3750	3700	2350	-	-
t, C	35	36,7	35,7	36,3	36,8	37,1	36,3	38,4	37,4
BP, mmHg	61/36	63/45	78/63	69/64	86/69	82/66	97/65	103/59	92/55
HR, min.	143	166	134	160	127	127	112	153	131
CVP, cmH2O (FV/IJV)	14/13	14/14	16/15	22/22	14/15	12//20	17/18	15/18	-/13
SO_2,%	83	82	89	76	93	/89	94	87	85
pO_2 (ABG), mmHg	53,7	55,5	41,2	46,2	54,8	51,4	52,6	54,5	46,8
pCO_2 (ABG), mmHg	43,9	50,1	43,6	57,1	40,3	42,8	44,6	39,5	37,7
FiO_2, %	60	100	100	80	60	65	50	40	10l mask
$etCO_2$	35	35	28	37	34	32	30	32	-
Dopamin, µg/kg/min	-	5	5	3	2	3	3	2,9	2
Milrinone, µg/kg/min	-	0,4	0,3	0,3	0,3	0,3	0,3	0,3	0,3
Adrenalin, µg/kg/min	0,07	0,15	0,16	0,05	0,03	0,02	0,008	-	-
Lactate, mmol/l	3,1	2,3	3	1,6	2,4	2,1	1,9	2	1,7

Table 12. The laboratory parameters during PediVas support. Gradually improvement of the white blood cells, urea, creatinine, protein, albumin, C-reactive protein and troponin I can be observed.

Parameters	**Day 1**	**Day 2**	**Day 3**	**Day 4**
White blood cells, 10^9/l	23,88	13,23	12,38	15,57
Hemoglobin, g/l	141	141	140,1	141,6
Platelets, 10^9/l	50	116	153,9	83,3
Urea, mmol/l	14,3	9,9	6,6	4,2
Creatinine, µmol/l	68	56	49	42
Total serum protein, g/l	39,7	49,6	-	61,7
Albumin, g/l	19,6	29	-	45,7
C-reactive protein, mg/l	29,8	22,4	-	1,99
Troponine I, µg/l	2,902	2,001	-	0,302
Activated clotting time, s	163	135	146	145

3.5. Successful childbirth after Fontan completion

One of the Fontan patients successfully delivered a baby. She is also the longest observed patient in the study.

Her initial diagnosis was tricuspid atresia and right ventricular hypoplasia. She underwent an atriopulmonary Fontan while she was 10 years old. The patient did not have any initial palliative procedures before. Few years later, she developed atrial fibrillation. The right atrium was significantly enlarged. Thirteen years later after the primary surgery the patient underwent Fontan conversion to TCPC with extracardiac ePTFE conduit. The main clinical indications for surgery were atrial fibrillation and initial signs of failing Fontan. Nine years after the conversion the patient successfully delivered a healthy baby via a caesarean section. At the last follow-up appointment, the patient was active in sinus rhythm with good blood pressure and oxygen saturation above 90%.

4. Discussion

Fontan operations have improved significantly over the past 30 years [21]. Our Centre's data showed that extracardiac TCPC with ePTFE conduit is a low-risk operation. Early and mid-term follow-up results are good. Advanced surgical techniques, lessons learned and improved patient care resulted in a better outcome. The long-term estimated survival rate after TCPC with extracardiac ePTFE conduit is 94 ± 3% at VUH SK. This data correlates with the results of recent studies [22].

The most common early and late complications were bleeding, arrhythmias, protein-losing enteropathy at our institution. The frequency and type of complications are similar with the results published by other authors [21, 23]. Several new studies highlight the importance of liver damage [24]. There was no severe liver impairment in our Centre. It may be due to underestimated liver fibrosis and no clear symptoms in our patients. Magnetic resonance elastography could accurately measure non-invasive subtle liver damage in Fontan patients [25].

Patients should be closely monitored for possible late complications. Increased systemic venous pressure and impaired cardiac function ultimately affect all patients with Fontan circulation [26]. The incidence of late complications in our Centre is small, but this can be linked to a relatively short average patient follow-up time (7.9 ± 6.6 years). Only one patient was observed for more than 26 years. The frequency of Fontan complications increases in the older age [26, 27]. Recent study recommends establishing multidisciplinary specialist centre for competent monitoring of Fontan patients throughout their lives [17].

The ideal age for the Fontan completion is not universally agreed so far. Some authors suggest this operation to perform earlier. This reduces the detrimental effect of cyanosis, improves physical capacity and blood circulation [13, 15]. Results of Fontan completion for patients under 3 years of age are good at our institution. None patient died in the early or late postoperative period. On the other hand, mortality was not statistically significant compared to the older group. Although three deaths were recorded in the latter. A larger sample of patients should be obtained for statistical significance. The rate of complications is small as well. It did not significantly differ from the older Fontan group.

According to our study, pleural effusion drainage was significantly shorter in younger patients after Fontan surgery. The median duration of drainage was 12 (IQR: 7 – 22) days. Patients who were older than 36 months at the time of the procedure had drains longer and median time was 22 (IQR: 16 – 33) days (Mann-Whitney U test, $p = 0.014$). Prolonged pleural effusion drainage is a rather typical symptom after Fontan surgery. It is believed that the cause is elevated systemic venous pressure [26]. According to the literature, reduced drainage in younger patients is a relatively new affirmation. Only few studies describe this finding.

Thromboembolism is a severe late complication, which can impair future prognosis of the Fontan patients [28]. Only two late thromboembolic events recorded in our institution. This could be due to anticoagulant treatment with warfarin at our centre. We start warfarin immediately after surgery and continue for 6 months. The dose of warfarin is adjusted according to the INR. The aim is to achieve a therapeutic target of 2. On the other hand, some of the thromboembolic events may be undiagnosed. Patients undergoing Fontan surgery may experience "secret" pulmonary thromboembolism without any significant symptoms. It affects Fontan circulation and resulting in increased PVR [29]. Chest MRI is a reliable study to diagnose asymptomatic thrombosis. It is important to carry out this study on a systematic basis [17]. The bleeding occurred only in the early period and was associated with the operation in our follow-up patients. The absence of this complication confirms that warfarin is given safely.

Most of the redo Fontan surgeries (9 out of 15) were performed on the patients from the atriopulmonary Fontan group. Dilated right atrium and arrhythmias have been the main triggers for Fontan conversion. Our data shows that these procedures can be performed with relatively low mortality. Even three patients out of six in Group III needed aortic homograft replacing with an extracardiac ePTFE conduit. This Fontan modification has been discontinued at our institution due to the high risk of aortic homograft stenosis. Three patients in Group IV needed replacement of extracardiac iPTFE conduit to a larger one. All of these patients were operated just shortly after introduction of extracardiac TCPC with ePTFE conduit in our centre. They had conduits size 16 mm in diameter. Subsequent results have shown that 18 mm or wider tubes do not induce stenosis. The 20 mm GORE-TEX® extracardiac conduit can be fashioned successfully even for a 14-month-old patient.

Currently, there are no generally accepted algorithms for the mechanical circulatory support in the case of acute severe cardiac failure. The use of mechanical assist devices for a short time as a bridge to recovery or for a longer time waiting for a transplant is a major challenge for the entire cardiac team [30]. We managed to wean off successfully one of our patient from VAD (Levitronix) as a bridge to recovery at our centre. The successful application of VAD could be beneficial for either short-term heart failure treatment or longer circulatory support awaiting cardiac transplantation.

The adult Fontan population is increasing due to improved survival. Some authors predict that the number of these patients will double in the next 20 years [31]. The need for competent medical care for these patients will increase. It is important that grown-up congenital heart specialists prepare for the life-long care of these patients in order to postpone complications and Fontan circulatory failure [17].

5. Study limitations

The biggest disadvantage of the research work is that the population consisted of patients operated in different surgical eras. Although Fontan circulation was created to all of the patients, the age at the procedure differed. Although all patients had functional single ventricle diagnosis, the heart defects were different.

This is a single centre study. The majority of patients were observed retrospectively following the history of illness and other medical records. Group II and Group III consisted of a small number of patients (4 and 6 respectively). The advance in surgical techniques and intensive care could have had an effect on the homogeneity of the results. Patients from Group IV are the last to be monitored. The follow-up time is shorter, so late follow-up results may not be completely accurate.

6. Conclusions

1. Fontan modification as TCPC with an extracardiac ePTFE conduit shows the best results.

2. Fontan completion with an extracardiac ePTFE conduit can be accomplished safe for patients under 3 years of age. Early and late results are favourable. Postoperative pleural effusion drainage is shorter for younger patients at Fontan completion.

3. Redo Fontan operations may be required in patients who have experienced arrhythmias with dilated atrium following atriopulmonary Fontan or have stenotic extracardiac Fontan conduit.

4. A ventricular assist device (Levitronix) can ensure effective cardiac support managing severe heart failure following Fontan completion.

5. Warfarin is an effective and safe medicine for prophylaxis of thrombosis.

7. Practical recommendations

1. Fontan patients should be monitored regularly at the multidisciplinary centre for life-long. Endocrinologists, gastroenterologists, pulmonologists and other specialist doctors in such a Centre, in addition to cardiac surgeons and cardiologists, should evaluate these patients.

2. Regular and up-to-date Fontan follow-up program should be introduced at VUH SK. Investigations should include TTE and ECG once a year, Holter monitoring and physical exercise test every 3 years, diagnostic cardiac catheter, cardiac MRI and liver biopsy 10 years after Fontan surgery.

3. The best prophylaxis for thrombotic events would be warfarin administration for the first half a year after Fontan completion. If no additional risk factors are discovered, aspirin is recommended instead of warfarin. If risk for thrombotic events is high, warfarin should be continued. The dose of warfarin should be titrated according to the INR with a target of two.

List of publications related to dissertation

1. Bezuska L, Lebetkevicius V, Lankutis K, Sudikiene R, Sirvydis VJ, Tarutis V. Fontan Completion for Younger than 3 Years of Age: Outcome in Patients with Functional Single Ventricle. Pediatr Cardiol. 2015;36(8):1680-4. doi: 10.1007/s00246-015-1217-2.

2. Bezuska L, Lebetkevicius V, Lankutis K, Tarutis V. Successful experience with Levitronix PediVAS for management of acute heart failure after Fontan surgery. Cent Eur J Med. 2012;7(4):529-32. doi: 10.2478/s11536-012-0005-0.

3. Bezuska L, Lebetkevicius V, Sudikiene R, Liekiene D, Tarutis V. 30-year experience of Fontan surgery: single-centre's data. J Cardiothorac Surg. 2017. doi:10.1186/s13019-017-0634-013019_2017_634. (Accepted but not published yet)

List of presentations related to dissertation

1. Bezuška L, Lebetkevičius V, Lankutis K, Sudikienė R, Tarutis V. Outcome in patients with functional single ventricle undergoing Fontan completion younger than 3 years of age. 24th Annual World Congress of the World Society of Cardiothoracic Surgeons, 06 - 10 September 2014, Switzerland, Geneva.

2. Bezuška L, Lebetkevičius V, Lankutis K, Sudikienė R, Liekiene D, Sirvydis VJ, Tarutis V. 30-year experience of Fontan surgery: single-centre's data. 25th Annual World Congress of the World Society of Cardiothoracic Surgeons, 19 - 22 September 2015, Scotland, Edinburgh.

3. Bezuška L, Sirvydis VJ. Fontan surgeries with ekstracardiac conduit in Lithuania: implimentation and results. Lithuanian Science Academy Conference of Junior scientists: „Biofuture: prospective of nature and life sciences", 2014, Vilnius.

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