Universiteit
Leiden
The Netherlands

Blood flow dynamics in the total cavopulmonary connection long-term after Fontan completion

Rijnberg, F.M.

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PART I

Long-term outcome after the Fontan procedure

CHAPTER 2

2

A 45-year experience with the Fontan procedure: tachyarrhythmia, an important sign for adverse outcome

Rijnberg FM, Blom NA, Sojak V, Bruggemans EF, Kuipers IM, Rammeloo LAJ, Jongbloed MRM, Bouma BJ, Hazekamp MG.

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Abstract

Objectives

This study aimed to evaluate our 45-year experience with the Fontan procedure and to identify risk factors for late mortality and morbidity.

Methods

Demographic, pre-, peri- and postoperative characteristics were retrospectively collected for all patients who underwent a Fontan procedure in a single-center between 1972-2016.

Results

The study included 277 Fontan procedures (44 atriopulmonary connections [APC], 28 Fontan-Björk, 42 lateral tunnels [LT] and 163 extracardiac conduits [ECC]). Early failure occurred in 17 patients (6.1%). Median follow-up of the study cohort was 11.9 years (Q_1-Q_3, 7.6-17.5). Longest survival estimates were 31% (95% CI, 18%-44%) at 35 years for APC/Björk, 87% (95% CI, 63%-96%) at 20 years for LT and 99% (95% CI, 96%-100%) at 15 years for ECC. Estimated freedom from Fontan failure (death, heart transplant, take-down, protein losing enteropathy, NYHA III-IV) at 15-years was 65% (95% CI, 52%-76%) for APC/Björk, 90% (95% CI, 73%-97%) for LT and 90% (95% CI, 82%-94%) for ECC. The development of tachyarrhythmia was an important predictor of Fontan failure (HR 2.6, 95% CI 1.2-5.8, P=0.017), thromboembolic/neurological events (HR 3.6, 95% CI 1.4-9.4, P=0.008) and pacemaker for sinus node dysfunction (HR 3.7, 95% CI 1.4-9.6, P=0.008). Prolonged pleural effusion (>21 days) increased risk of experiencing PLE (HR 4.7, 95% CI 2.0-11.1, P<0.001).

Conclusions

With modern techniques, survival and freedom from Fontan failure is good. However, Fontan patients remain subject to general attrition. Tachyarrhythmia is an important sign for adverse outcome. Prevention and early treatment of tachyarrhythmia may therefore be paramount for improving long-term outcome.

Introduction

The Fontan procedure is the current palliative treatment of single ventricle anomalies. The surgical technique has evolved from the atriopulmonary connection (APC) or Fontan-Björk modification (right atrium to right ventricle), via the intracardiac lateral tunnel (LT) to the extracardiac conduit (ECC) procedure, which is nowadays the preferred approach in most centers. Early Fontan failure has reduced from 27% in early experiences[1, 2] to 4% in a recent ECC cohort [3], with low perioperative mortality rates of 0.5-1% [3, 4]. Mid-term and long-term outcomes with the newer Fontan techniques are good, with 15-year and 20-year survival rates of 85-96% [4-6] and 76-79% [6, 7], respectively.

As the number of survivors of the Fontan procedure expands, information on long-term outcomes in patients with the various approaches of the Fontan palliation becomes increasingly valuable [8-11]. In this study, we report our 45-year experience with the Fontan procedure and aim to identify factors associated with late mortality and morbidity.

Materials and Methods

We conducted a retrospective study of 277 consecutive patients who underwent a Fontan procedure (excluding Kawashima procedures) at Leiden University Medical Center, the Netherlands (1972-2016). Fontan procedures consisted of 44 APC, 28 Fontan-Björk, 42 LT and 163 ECC procedures. In further analyses, APC and Fontan-Björk procedures were combined. APC/Fontan-Björk was the preferred technique between 1972-1990 (96%), LT between 1991-1999 (67%) and ECC between 2000-2016 (91%). All data were obtained from (referring) hospital records and were analysed for demographic, pre-, peri- and postoperative characteristics until last follow-up. The Hospital Medical Ethical Committee approved the study.

Definitions

Early outcomes were defined as events occurring before hospital discharge or within 30 days and late outcomes as events occurring after initial hospital discharge.

Fontan failure was defined as death, heart transplantation, Fontan take-down, protein losing enteropathy (PLE) or plastic bronchitis, or *New York Heart Association* (NYHA) class III-IV. The diagnosis of PLE was based on loss of alpha-1-antitrypsin in the stool or by the combination of low albumin/total protein with generalised edema. The diagnosis of plastic bronchitis was based on the expectoration of bronchial casts. In further analyses, PLE and plastic bronchitis were combined. Prolonged pleural effusion (PE) was defined as an effusion duration needing drains >21 days. First occurrence of a clinically relevant

arrhythmia was defined by the need of antiarrhythmic medication, electrical cardioversion or pacemaker (PM) placement. Tachyarrhythmia included atrial fibrillation, atrial flutter, other supraventricular tachycardias and ventricular tachycardia. Bradyarrhythmia was defined as sinus node dysfunction (SND) or complete atrioventricular block (described separately) requiring PM. Thromboembolic event (TE) was defined as a thrombus in the Fontan pathway (superior vena cava/Fontan tunnel/right atrium) or pulmonary embolism. Neurological event (NE) was defined as a cerebral vascular accident (CVA), ischemic or haemorrhagic. Surgical reinterventions included all Fontan related interventions including first PM implantations but excluding PM replacements. Early resternotomies (bleeding/tamponade) were excluded. The combined outcome for Fontan-related morbidity consisted of Fontan failure, tachyarrhythmia, bradyarrhythmia or TE/NE. Systolic cardiac function and atrioventricular valve (AVV) regurgitation were assessed qualitatively from echocardiographic reports. Systolic function was graded as good/mildly impaired, moderate or poor. Significant AVV-regurgitation was defined as ≥moderate-severe. NYHA-class was assessed by review of the medical records. Liver fibrosis/cirrhosis was based on findings of ultrasound, magnetic resonance imaging or computed tomography reports or from autopsy findings.

Statistical analyses

Continuous data are presented as median (first to third quartile [Q_1-Q_3]). Categorical data are presented as number and percentage. Early outcome was described for the whole cohort. Late outcome was reported for hospital survivors with intact Fontan circulation (no take-down) only. Late survival and freedom from late morbidity rates were estimated using the Kaplan-Meier method and reported as percentages with asymmetrical 95% confidence intervals (CI). Kaplan-Meier curves were created for each Fontan group according to the initial Fontan technique and equality of the survival distributions was tested using the log-rank test. Possible predictors of late mortality and morbidity endpoints were tested using univariable and multivariable (enter method) Cox regression models. Analysed endpoints included mortality, Fontan failure, PLE/plastic bronchitis, tachyarrhythmia, bradyarrhythmia, TE/NE and the combined outcome for Fontan-related morbidity. Variables included in the univariable Cox regression models are mentioned in Table 1, with the addition of prolonged PE and first occurrence of the events PLE, tachyarrhythmia, bradyarrhythmia and TE/NE. These possible intermediate events were treated as time-dependent covariates. The LT and ECC groups were combined in the Cox regression analyses due to the limited amount of events in each subgroup. Age was divided into three age groups that were considered clinically relevant: <4 years, 4-8 years and >8 years. Variables with a P-value <0.15 in univariable analyses were included in the multivariable models. The proportional hazards assumption was tested for each variable using time-dependent covariates. For the tachyarrhythmia, bradyarrhythmia, TE/NE and PLE endpoints, a patient was

censored when death, heart transplant or Fontan take-down occurred before the event. The influence of ventricular morphology on late outcome was tested in both the total study cohort and the LT/ECC group only, since the predominance of left ventricular morphology in the APC/Björk group could mask the effect of ventricular morphology on late outcome. Because fenestration was introduced after the introduction of the LT technique, the effect of fenestration on endpoints was tested in the LT/ECC group only. A P-value of <0.05 (two-sided) was considered statistically significant. Data were analysed and displayed with SPSS 24.0 (IBM-SPSS, NY, USA) or Prism 7.0 (GraphPad, CA, USA).

Results

Study population

The focus of this study was on late events in hospital survivors with intact Fontan circulation (study cohort). Demographics and patient characteristics of the study cohort are detailed in Table 1. Complete follow-up was available for 94% of patients (median, 11.9 years; Q_1-Q_3, 7.6-17.5). Fifteen patients were lost to follow-up (median time after Fontan completion, 10 months; Q_1-Q_3, 41 days-3.9 years).

Early outcomes for the whole cohort

Early failure occurred in 17 patients (6.1%, median 3 days, Q_1-Q_3 1-26 days): 11 deaths (5 APC/Björk [6.9%], 4 LT [9.5%], 2 ECC [1.2%]) and 7 take-downs (1 LT [2.4%], 6 ECC [3.7%]). One patient died shortly after early take-down. Five patients (1.8%) had an early TE. Sixteen patients (5.8%) had an early NE (15 ischemic, 1 haemorrhagic). Prolonged PE occurred in 46 patients (18%). Since 2000, the year in which the ECC technique was introduced, early failure improved from 9.3% to 4.1%, early mortality from 8.3% to 1.2%, early TE from 3.6% to 1.2% and early NE from 11.6% to 3.0%.

Table 1. Patient demographics and characteristics of hospital survivors with intact Fontan circulation

Characteristic	APC/Björk* (n=67)	LT* (n=38)	ECC* (n=155)
Male*, n(%)	39(58)	22(58)	93(60)
Age at Fontan*, years, median(Q_1-Q_3)	8.1(4.9-14.2)	4.3(2.8-6.0)	3.5(3.0-4.3)
Dextrocardia*, n(%)	7(10)	9(24)	5(3)
Heterotaxy*, n(%)	0(0)	7(18)	6(4)
Common AVV*, n(%)	1(2)	3(8)	15(10)
TAPVD/PAPVD*, n(%)	0(0)	3(8)	5(3)
Ventricular morphology*, n(%)			
Left ventricle	61(91)	26(68)	77(50)
Right ventricle	4(6)	10(26)	60(39)
Biventricular/indeterminate	2(3)	2(5)	18(12)
Morphological group, n(%)			
DILV	13(19)	9(24)	27(17)
DORV	0(0)	2(5)	17(11)
TA	50(75)	10(26)	31(20)
HLHS*	0(0)	0(0)	35(23)
ccTGA	3(5)	5(13)	11(7)
TGA	1(2)	2(5)	2(1)
PA+IVS	0(0)	5(13)	13(8)
Unbalanced AVSD+DORV	0(0)	1(3)	6(4)
Unbalanced AVSD	0(0)	0(0)	9(6)
Other	0(0)	4(11)	4(3)
Procedures pre-Fontan, n(%)			
Number of surgical procedures, mean(SD)	1.0(0.8)	1.7(0.8)	2.2(0.7)
Systemic-pulmonary shunt*	37(55)	16(42)	94(61)
PA banding*	6(9)	8(21)	42(27)
Prior/concomitant PA stent/reconstruction*	12(18)	4(11)	31(20)
Prior/concomitant AVV repair/replacement*	1(2)	4(11)	27(17)
Glenn shunt*	15(22)	32(84)	155(100)
Age at Glenn, years, median(Q_1-Q_3)	2.1(0.8-3.5)	1.9(0.9-3.8)	0.6(0.4-1.1)
Pre-Fontan characteristics			
Oxygen saturation**(%), n=217, median(Q_1-Q_3)	82(78-85)	84(78-85)	81(78-84)
Mean PAP** n=229, mmHg, median(Q_1-Q_3)	10(9-15)	9(8-12)	11(9-12)
≥moderate systolic dysfunction, n(%)	1(3)	1(3)	0(0)
AVV regurgitation* (≥moderate-severe), n(%)	0(0)	5(15)	13(9)
Fontan characteristics			
CPB time** n=190, minutes, median(Q_1-Q_3)	137(106-205)	119(82-214)	95(76-126)
Cross clamp time** n=201, minutes, median(Q_1-Q_3)	73(56-124)	67(56-99)	15(0-47)
Age at Fontan*, years, median(Q_1-Q_3)	8.1(4.9-14.2)	4.3(2.8-6.0)	3.5(3.0-4.3)
Fenestration*, n(%)	1(2)	26(68)	109(70)
Age at last FU with intact Fontan circulation***, years, median(Q_1-Q_3)	29.5(19.3-42.2)	22.9(15.8-25.9)	12.9(10.0-16.2)

*Variables included in the univariable Cox regression models **not included in the univariable Cox regression models due to missing data. ***Censored at death, heart transplant or take-down.

AVV, atrioventricular valve; T(P)APVD, total (partial) anomalous pulmonary venous drainage; DILV, double inlet left ventricle; DORV, double outlet right ventricle; TA, tricuspid atresia; HLHS, hypoplastic left heart syndrome; ccTGA, congenital corrected transposition of the great arteries; PA+IVS, pulmonary atresia+intact ventricular septum; AVSD, atrioventricular septal defect; PA(P), pulmonary artery (pressure); CPB, cardiopulmonary bypass

Table 2. Modes of late death

Late mortality	43
Fontan failure with preserved systolic ventricular function	16
-Pneumonia	3
-Fontan pathway obstruction/dysfunction	5
-TE	4
-Peri-procedural after reintervention for Fontan failure with preserved systolic ventricular function	4
Fontan failure with poor systolic ventricular function	4
Peri-procedural after other reintervention	2
Sudden death	6
Neurological event	2
Sepsis	3
Other	6
Unknown	4

Late outcomes in the study cohort

Survival

There were 43 late deaths (median age 26.8 years, Q_1-Q_3, 18.5-38.8). Modes of late death are described in Table 2. One patient received a heart transplantation 10 months after Fontan completion. The estimated overall survival rate after the Fontan procedure was 70% (95% CI, 56%-80%), 63% (95% CI, 49%-74%), 52% (95% CI, 38%-64%) and 31% (95% CI, 18%-44%) at 15, 20, 30 and 35 years, respectively, in the APC/Björk group, 97% (95% CI, 79%-100%) and 87% (95% CI, 63%-96%) at 15 and 20 years, respectively, in the LT group and 99% (95% CI, 96%-100%) at 15 years in the ECC group (Figure 1A; P<0.001). APC/Björk type of Fontan (HR, 4.6; 95% CI, 1.2-17.5; P=0.024) and occurrence of TE/NE (HR, 16.8; 95% CI, 7.7-37.1; P=0.002) were independent risk factors for late death (Supplemental table A). Fenestration was not associated with late death or any other analysed endpoints.

Fontan failure

Late failure of the Fontan circulation occurred in 59 patients. First failure event was death (n=28), PLE (n=26), NYHA class III/IV (n=3), take-down (n=1) or heart transplantation (n=1). Freedom from Fontan failure rate was 65% (95% CI, 52%-76%), 57% (95% CI, 43%-68%) and 44% (95% CI, 31%-56%) at 15, 20 and 30 years, respectively, in the APC/Björk group, 90% (95% CI, 73%-97%) at 15 and 20 years in the LT group and 90% (95% CI, 82%-94%) at 15 years in the ECC group (Figure 1B; P<0.001). APC/Björk type of Fontan (HR 3.4; 95% CI, 1.2-9.4; P= 0.020), tachyarrhythmia (HR, 2.6; 95% CI, 1.2-5.8; P =0.017), TE/NE (HR, 9.3; 95% CI, 4.1-21.2; P<0.001) and prolonged PE (HR, 2.7; 95% CI, 1.3-6.0; P=0.011) were independent risk factors for late Fontan failure (Supplemental table A). Ventricular

morphology (right (excluding HLHS) versus left functional ventricle) was not associated with late Fontan failure, neither in the total study cohort nor in the LT/ECC group only.

Arrhythmia

Tachyarrhythmia

Three patients had pre-Fontan periods of sustained tachyarrhythmia and were excluded from tachyarrhythmia endpoint analysis. Fifty-nine patients developed a tachyarrhythmia after a median of 10.8 years (Q_1-Q_3, 4.8-16.9). Freedom from tachyarrhythmia rate was 46% (95% CI, 32%-58%) and 24% (95% CI, 11%-34%) at 15 and 20 years, respectively, in the APC/Björk group, 81% (95% CI, 62%-90%) at 15 and 20 years in the LT group and 94% (95% CI, 87%-98%) at 15 years in the ECC group (Figure 1C; P<0.001). Post hoc log-rank analysis between LT and ECC groups showed a significantly lower freedom from tachyarrhythmia in the LT group (P=0.022), which occurred predominantly within the first 5 years (all atrial flutter). APC/Björk type of Fontan (HR, 5.1; 95% CI 2.1-12.7; P<0.001), age at Fontan >8 years (HR, 3.0; 95% CI, 1.4-6.9; P=0.001) and common AVV (HR, 9.0; 95% CI, 3.0-27.3; P<0.001) were independent predictors of occurrence of tachyarrhythmia (Supplemental table A).

Bradyarrhythmia

Twenty-three patients received a PM for SND, of which 2 at the time of the Fontan procedure and were excluded from the analysis. Freedom from PM for SND rate was 94% (95% CI, 84%-98%), 86% (95% CI, 72%-94%) and 69% (95% CI, 51%-82%) at 10, 20 and 30 years, respectively, in the APC/Björk group; 90% (95% CI, 73%-97%) and 87% (95% CI, 69%-95%) at 10 and 20 years, respectively, in the LT group and 95% (95% CI, 89%-98%) at 10 years in the ECC group (Supplemental figure 1A; P=0.600). Tachyarrhythmia was the only risk factor for PM for SND (HR, 6.0; 95% CI, 1.8-19.6; P=0.008) (Supplemental table A).

Complete AV block

Two patients needed a PM for complete AV block before the Fontan procedure. Eleven patients (4%) needed a PM for complete AV block at a median of 5.5 years (Q_1-Q_3, 22 days-20.7 years) after the Fontan procedure, which were mostly related to tricuspid valve interventions (3/11) or ablation therapy (3/11).

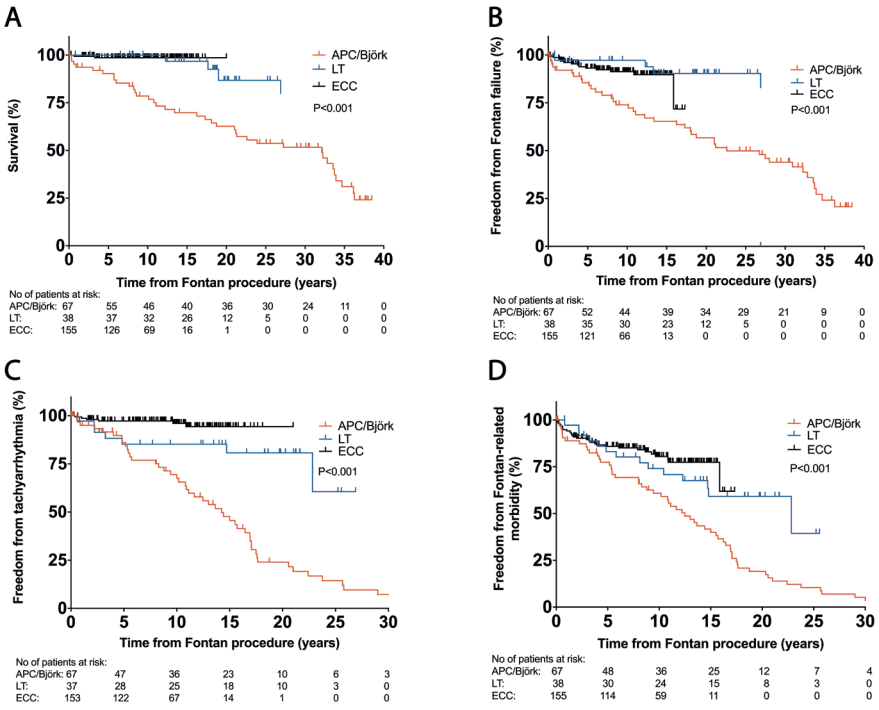

Figure 1. Kaplan-Meier curves per Fontan group (hospital survivors) for overall survival (A), freedom from Fontan failure (B), freedom from tachyarrhythmia (C) and combined outcome for Fontan-related morbidity (D). P-values of the log-rank tests between groups are indicated in the graphs.

APC; atriopulmonary connection, LT; lateral tunnel, ECC; extracardiac conduit

Thromboembolic and neurological events

Late TE occurred in 20 patients after a median of 10.4 years (Q_1-Q_3, 3.6-22.0). Site of thrombus was right atrium (n=10), pulmonary embolism (n=10), Fontan tunnel (n=3) and superior vena cava (n=3). Anticoagulant medication at time of TE was oral anticoagulation (OAC) in 8 patients, platelet inhibitor in 2 or none (n=7). In 3 patients, the event occurred shortly after reintervention. Fifteen patients experienced a late NE (12 ischemic, 3 haemorrhagic). Of the 12 ischemic CVAs, 4 occurred shortly after reintervention and 1 post-partum. The other 7 patients were on OAC (n=1), platelet inhibitors (n=3), no anticoagulation (n=2) or unknown anticoagulation (n=1). All patients with a haemorrhagic CVA were on OAC. Freedom from late TE/NE rate was 81% (95% CI, 68%-89%), 72% (95% CI, 58%-82%) and 60% (95% CI 45%-72%) at 15, 20 and 30 years, respectively, in the APC/Björk group, 89% (95% CI, 70%-96%) at 15 and 20 years in the LT group and 93% (95% CI, 85%-97%) at 15 years in the ECC group (Supplemental

figure 1B; P=0.082). Tachyarrhythmia was the only risk factor for TE/NE (HR, 3.6; 95% CI, 1.4-9.4; P=0.008) (Supplemental table A).

PLE

Twenty-six patients developed PLE at a median of 4.4 years (Q_1-Q_3, 1.5-8.7) after the Fontan procedure (median age at diagnosis of PLE 10.6 years, Q_1-Q_3 6.7-16.8). Freedom from PLE rate was 88% (95% CI, 82%-92%) and 82% (95% CI, 69%-89%) at 20 and 30 years, respectively. Patients were not divided into Fontan subgroups due to low event numbers. Survival after diagnosis of PLE was 60% (95% CI, 37%-77%) at 5 years (Figure 2). The occurrence of PLE appeared to be related to Fontan tunnel obstruction/dysfunction (n=8), pulmonary artery stenosis/hypoplasia (n=5), ≥moderate AVV regurgitation (n=5), pneumonia episode (n=3), bradyarrhythmia (n=2) or diaphragm paresis (n=1). In 6 patients, no clear contributions could be identified. Prolonged PE was an independent risk factor for occurrence of PLE (HR, 4.7; 95% CI, 2.0-11.1; P<0.001) (Supplemental table A).

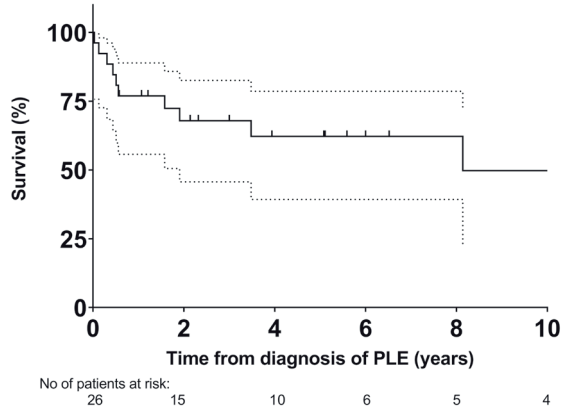

Figure 2. Kaplan-Meier curve for survival after the diagnosis of PLE/plastic bronchitis. Dashed lines indicate 95% confidence intervals.

Thirteen patients with PLE underwent surgical/percutaneous reintervention and 9 patients received conservative treatment. Two patients died early after initial hospital admission and treatment information was missing in 2 patients. (Transient) resolution of PLE occurred in 8 patients (31%). In 2 patients, in whom PLE was triggered by a pneumonia episode, resolution occurred after recovery of the pneumonia but with regular PLE exacerbations during recurrent infectious episodes.

Combined outcome for Fontan-related morbidity

The combined outcome for Fontan-related morbidity (i.e. Fontan failure, tachyarrhythmia, bradyarrhythmia or TE/NE) occurred in 101 patients. Freedom from the combined outcome rate was 40% (95% CI, 28%-52%) and 19% (95% CI, 10%-30%) at 15 and 20 years, respectively, in the APC/Björk group, 59% (95% CI, 40%-74%) at 15 years in the LT group and 77% (95% CI, 68%-86%) at 15 years in the ECC group (Figure 1D; P<0.001). APC/Björk type of Fontan (HR, 2.4; 95% CI, 1.2-4.8; P =0.016), common AVV (HR, 3.2; 95% CI, 1.4-7.1; P=0.006), total/partial anomalous pulmonary venous drainage (TAPVD/PAPVD) (HR, 5.2; 95% CI, 1.3-20.2; P=0.018) and prolonged PE (HR, 1.9; 95% CI, 1.1-3.4; P=0.020) were independent risk factors for the combined adverse events (Supplemental table A).

Surgical reinterventions

Seventy-seven patients underwent 109 surgical reinterventions (Supplemental table B). Freedom from surgical reintervention rate was 54% (95% CI, 40%-66%), 40% (95% CI, 27%-53%) and 25% (95% CI, 14%-38%) at 15, 20 and 25 years, respectively, in the APC/Björk group, 60% (95% CI, 41%-74%) at 15 and 20 years in the LT group and 83% (95% CI, 74%-89%) at 15 years in the ECC group (Supplemental figure 1C; P<0.001). The high incidence of surgical reinterventions in the LT group was mainly caused by PM placements (n=9, 50%).

Percutaneous reinterventions

Thirty-two patients underwent 52 catheter interventions after a median of 5.9 years (Q_1-Q_3, 1.8-17.4), excluding routine fenestration closures (Supplemental table C).

Status at last follow-up

At last follow-up, 200 patients were alive with an intact Fontan circulation (median time after Fontan completion, 11.5 years; Q_1-Q_3, 7.6-15.6.), with 88% of these patients in NYHA class 1. Medication status at last follow-up (n=196) included ACE-inhibitors (n=19, 10%), ≥1 antiarrhythmics (n=26, 13%), ≥1 diuretics (n=21, 11%) and pulmonary vasodilator therapy (n=6, 3%). Of the patients <18 years, 105 (78%) were on platelet inhibitors and 30 were on OAC (22%). In the adult patients, 21 were on platelet inhibitors (34%), 37 were on OAC (61%), 1 patient received NOAC (2%) and 2 patients (3%) received no anticoagulation.

Ventricular systolic function (n=199) at last follow-up (median time after Fontan completion, 10.5 years; Q_1-Q_3, 6.6-14.6) was good-mildly impaired (n=188), moderately impaired (n=9) or poor (n=2). Fourteen out of 195 patients (7.2%) with known neurological status at last follow-up had severe neurological deficits due to prior CVA. In the total study cohort, liver cirrhosis was identified in 16 patients, fibrosis in 3 and

hepatocellular carcinoma in 1 patient (median time after Fontan procedure, 20.5 years; Q_1-Q_3, 16.5-26.8).

Discussion

Early outcomes of the Fontan procedure are nowadays good. We observed a 1.2% perioperative mortality rate and 3.7% early take-down rate in our ECC cohort, in line with the literature[3, 4]. However, insight in long-term outcome and risk factors for late adverse events becomes increasingly important for the expanding cohort of adult Fontan patients.

Late survival and Fontan failure

Late survival in contemporary Fontan cohorts is good, with a reported survival rate of 70-91% after 20 years (LT)[6, 8, 12] and 93-98% after 15 years (ECC)[4, 5]. This is in line with our experience, with a late survival rate in hospital survivors of 87% after 20 years (LT) and 99% after 15 years (ECC). Failure of the Fontan circulation with preserved ventricular systolic function was the predominant mode of death. These patients presented with right heart failure symptoms often unresponsive to diuretics and with good or only mildly impaired systolic ventricular function, in whom increased resistance of the Fontan pathway (e.g. pulmonary embolism, stenosis of a valve(d conduit) used in some APC patients, compression of RA-RV conduits) seemed to be responsible for the failure of the Fontan circulation. However, we could not exclude diastolic dysfunction as a mode of Fontan failure, as diastolic function was rarely reported.

The APC and Björk-Fontan techniques are nowadays abandoned, as dilatation of the incorporated atrium is known to result in a high incidence of arrhythmias and energy dissipating turbulent flow[13, 14]. Thirty-year survival rates after APC Fontan are scarce and vary between 41%-69%[8, 11]. We observed a 30-year survival rate of 52% in our APC/Björk cohort, and our data showed a nearly linear survival curve, suggesting that long-term survival >50 years after the Fontan procedure will probably be rare in this group of patients. Of note, the APC/Björk cohort received their Fontan completion at an older age (median, 8.1 years versus 4.3 [LT] and 3.5 [ECC]), which should be kept in mind when comparing the curves. We identified APC/Björk type of Fontan and TE/NE to be risk factors for late death and APC/Björk type of Fontan, tachyarrhythmia, TE/NE and prolonged PE were risk factors for late Fontan failure. The association of tachyarrhythmia and TE/NE with late Fontan failure is in line with others[11, 12, 15].

Late morbidity

Arrhythmia

In our experience, APC/Björk type of Fontan, age >8 years and common AVV were predictors of late tachyarrhythmia. Although the incidence of tachyarrhythmia has reduced with the LT and ECC techniques, these patients are still subject to a gradual increase of tachyarrhythmia over time[12, 15]. The presumed superiority of the ECC over the LT technique in terms of avoiding tachyarrhythmia has been a matter of debate, although a recent meta-analysis supported this assumption[16]. In our experience, LT patients seemed to have a higher risk of tachyarrhythmia compared to ECC patients. However, group and event numbers were relatively small and the higher incidence of heterotaxia (18% [LT], versus 4% [ECC]), which has been associated with an increased risk of tachyarrhythmia[12], might have influenced outcome. Tachyarrhythmia is not tolerated well and can lead to haemodynamic deterioration, increased venous pressures and increased risk of TE events[12, 17, 18]. With the deleterious effects of tachyarrhythmia on long-term outcome in Fontan patients becoming more clear[11, 12, 15], avoidance of this complication is important.

To minimize the risk of developing supraventricular tachyarrhythmia, we prefer to use the extracardiac TCPC in order to minimize atrial suture lines, prevent atrial dilatation and minimize the risk of sinus node dysfunction. When tachyarrhythmia occurs, early and aggressive treatment may be paramount to improve long-term outcome for these patients. Treatment can range from medication and ablation therapy, antitachycardia pacemaker therapy to Fontan conversion with concomitant MAZE surgery for selected cases (APC/LT) with therapy resistant tachyarrhythmia.

In our experience, freedom of PM for SND was generally good. Tachyarrhythmia was associated with the need of a PM for SND. This association can be explained by the increased incidence of late SND in our APC/Björk cohort, which appeared to be iatrogenically caused by the need for antiarrhythmic medication.

Thromboembolic and neurological events

The risk of TE/NE has significantly decreased with the introduction of the LT and ECC techniques. In our experience, tachyarrhythmia was a risk factor for TE/NE, an association also recently described by Wilson et al.[12]. This even more emphasises the importance of avoiding tachyarrhythmias in Fontan patients, especially as the occurrence of TE/NE was a strong predictor of death in our cohort. Our anticoagulation protocol in the modern cohort is to start with OAC for the first 3-12 months postoperatively, which is subsequently changed to antiplatelet therapy only. At adult age the majority of patients switch to OAC.

PLE

Freedom from PLE rate at 20 years was 88%, similar to the 88-89% observed in previous large cohorts[8, 15], and 5-year mortality after diagnosis of PLE was 40%. Only 31% of patients had (transient) resolution of PLE symptoms, emphasising the need for better treatment options. While the pathogenesis of PLE is not fully clarified, increased central venous pressure is an important factor[19], and therefore factors leading to increased resistance may trigger PLE. We had several cases in which PLE (transiently) resolved after Fontan tunnel replacement or after resolution of a pneumonia episode. We speculate that pneumonia can cause increased pulmonary vascular resistance, leading to increased central venous pressure, thereby triggering PLE episodes in some patients. Prolonged PE was strongly associated with occurrence of PLE in our study, in concordance with previous studies[15, 20]. Future focus on these patients with prolonged PE may aid in our understanding of PLE, which is essential to improve treatment and outcome.

Combined outcome for Fontan-related morbidity

While the occurrence of the combined outcome for Fontan-related morbidity events (i.e., Fontan failure, arrhythmia or TE/NE) has decreased with modern techniques, our data showed that general attrition remains present, with a nearly linear trend over time. At 15 years, 41% (LT) and 23% (ECC) of patients had experienced one or more adverse events.

Surgical reinterventions

Freedom from surgical reintervention for the modern cohort (LT/ECC) has increased significantly compared with our early APC/Björk cohort. Most of these latter patients (57%) were reoperated for compression, severe regurgitation or stenosis of the RA-RV (Björk-Fontan) conduit or for stenotic valves used in some APC patients. Only 4 (3%) ECC patients required conduit replacement/stent placement due to small tunnel size or stenosis. Pacemaker was the most common reintervention in the LT/ECC cohort, accounting for 50% and 25% of the surgical procedures, respectively.

Limitations and strengths

This study is limited by its retrospective character. Also, some variables (e.g. pre-operative haemodynamics) could not be included in the analysis due to missing data in the older cohort. Furthermore, our study may have been underpowered to assess the influence of some variables on long-term outcome. Relatively low numbers of events occurred in the modern cohort of LT/ECC patients. Finally, the different Fontan techniques also represent different surgical eras and this should be kept in mind when interpreting the results. Liver examinations were not routinely performed and results therefore do not represent the incidence of liver fibrosis/cirrhosis in Fontan patients.

Strength of our study is its very long-term follow-up with 94% completeness. Additionally, the majority of hospital survivors (86%) received routine follow-up at the Center for Congenital Heart Disease Amsterdam-Leiden, which ensured the inclusiveness of data.

Conclusion

In the current era, the majority of patients survive into adulthood. Implementation of the LT/ECC techniques has significantly delayed the development of late complications, however, Fontan patients remain subject to gradual attrition. The incidence of PLE remained substantial in our ECC cohort and patients with prolonged pleural effusions carry the highest risk for developing PLE. The occurrence of tachyarrhythmia is an important sign for adverse outcome. Prevention and early treatment may therefore be paramount for improving the long-term outcome of Fontan patients.

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Supplementary materials

Supplemental table A. Results of the multivariable Cox Regression* analyses for late outcome

Variable	HR	95% CI	P-value
Mortality			
APC/Björk (vs LT/ECC)	4.6	1.2-17.5	**0.024**
Age at Fontan >8 years (vs <4 years)	1.7	0.5-5.5	0.357
Glenn	0.5	0.2-1.3	0.158
Tachyarrhythmia	1.4	0.5-3.8	0.396
TE/NE	16.8	7.7-37.1	**0.002**
PLE	2.2	0.9-5.5	0.082
Fontan Failure			
APC/Björk (vs LT/ECC)	3.4	1.2-9.4	**0.020**
Age at Fontan >8 years (vs <4 years)	1.7	0.7-4.3	0.282
Female sex	0.7	0.4-1.3	0.256
Glenn	1.5	0.7-3.5	0.325
Tachyarrhythmia	2.6	1.2-5.8	**0.017**
TE/NE	9.3	4.1-21.2	**<0.001**
Prolonged PE (>21 days)	2.7	1.3-6.0	**0.011**
Tachyarrhythmia			
APC/Björk (vs LT/ECC)	5.1	2.1-12.7	**<0.001**
Age at Fontan >8 years (vs <4 years)	4.0	1.8-9.1	**0.001**
Common AVV	9.0	3.0-27.3	**<0.001**
Glenn	0.7	0.4-1.4	0.279
Bradyarrhythmia			
Tachyarrhythmia	3.7	1.4-9.6	**0.008**
TE/NE			
APC/Björk (vs LT/ECC)	1.3	0.5-3.4	0.545
Age fontan >8 years (vs <4 years)	2.0	0.7-5.4	0.177
Dextrocardia	0.2	0.0-1.5	0.126
Tachyarrhythmia	3.6	1.4-9.4	**0.008**
PLE			
Female sex	0.5	0.2-1.2	0.134
Prolonged PE (>21 days)	4.7	2.0-11.1	**<0.001**
Combined outcome for Fontan related morbidity			
APC/Björk (vs LT/ECC)	2.4	1.2-4.8	**0.016**
Age at Fontan >8 years (vs <4 years)	1.8	1.0-3.3	0.061
Heterotaxia	0.8	0.2-2.8	0.759
Common AVV	3.2	1.4-7.1	**0.006**
TAPVD/PAPVD	5.2	1.3-20.2	**0.018**
Glenn	0.8	0.4-1.4	0.396
Prolonged PE (>21 days)	1.9	1.1-3.4	**0.020**

* Enter method. All variables included in the multivariable Cox regression models are shown.

APC, atriopulmonary connection; ECC, extracardiac conduit; LT, lateral tunnel; PLE, protein losing enteropathy; PE, pleural effusion; TE, thromboembolic; NE, neurological event; AVV, atrioventricular valve.

Supplemental Table B. Surgical reinterventions per type of Fontan

APC/Björk (n=43)	69
-Redo Fontan	39
-Conversion to TCPC	15
-PM placement*	16
-Other	7
LT (n=14)	18
-PM placement	9
-Redo Fontan	3
-Conversion to ECC	2
-Other	4
ECC (n=20)	24
-PM placement	6
-LVOTO relief	4
-Take-down	3
-Redo Fontan	3
-PA/Glenn plasty	2
-Other	6

Values are numbers.

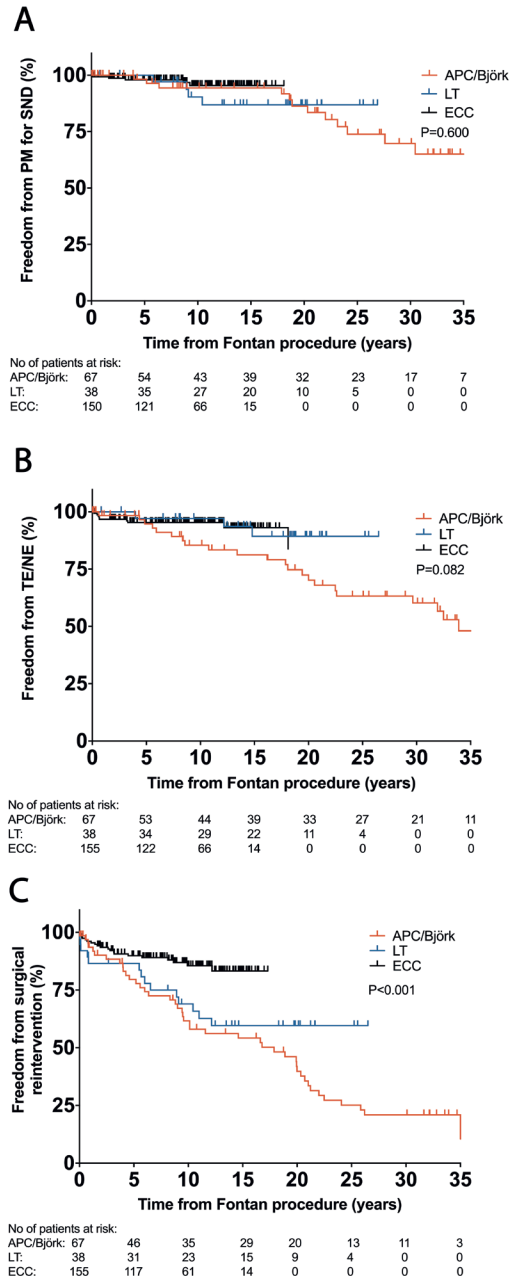
*Some PM placements were concomitant with a Fontan conversion or redo.

APC, atriopulmonary connection; LT, lateral tunnel; ECC, extracardiac conduit; TCPC, total cavopulmonary connection; PM, pacemaker; LVOTO, left ventricular outflow tract obstruction; PA, pulmonary artery

Supplemental Table C. Percutaneous reinterventions

Type of reintervention	52
-Veno-venous collateral coiling	10
- Aorto-pulmonary collateral coiling	6
-Pulmonary artery stent placement	6
- Fontan conduit stent placement	3
-Dilatation of stent	8
- Dilatation of aortic arch	1
- Valve placement in Björk conduit	3
- Ablation	7
-Other	8

Values are numbers.



Supplemental Figure 1. Kaplan-Meier curves per Fontan group (hospital survivors) for freedom from PM for SND (A), TE/NE (B) and surgical reinterventions (C). P-values of the log-rank tests between groups are indicated in the graphs.

APC; atriopulmonary connection, LT; lateral tunnel, ECC; extracardiac conduit, PM; pacemaker, SND; sinus node dysfunction, TE/NE; thromboembolic event/neurological event