European Journal of Cardio-Thoracic Surgery 46 (2014) 465–473
doi:10.1093/ejcts/ezu015 Advance Access publication 26 February 2014

ORIGINAL ARTICLE

The extracardiac conduit Fontan procedure in Australia and New Zealand: hypoplastic left heart syndrome predicts worse early and late outcomes†

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Received 1 October 2013; received in revised form 19 December 2013; accepted 30 December 2013

Abstract

OBJECTIVES: To identify factors associated with hospital and long-term outcomes in a binational cohort of extracardiac conduit (ECC) Fontan recipients.

METHODS: All patients who underwent an ECC Fontan procedure from 1997 to 2010 in Australia and New Zealand were identified, and perioperative, follow-up, echocardiographic and reintervention data collected. Risk factors for early and late mortality, failure and adverse outcomes were analysed.

RESULTS: A total of 570 patients were identified, and late follow-up was available in 529 patients. The mean follow-up was 6.7 years (standard deviation: 3.5) and completeness of the follow-up was 98%. There were seven hospital mortalities (1%) and 21 patients (4%) experienced early failure (death, Fontan takedown/revision or mechanical circulatory support). Prolonged length of stay occurred in 10% (57 patients), and prolonged effusions in 9% (51 patients). Overall survival at 14 years was 96% (95% confidence interval [CI]: 93–98%), and late survival for patients discharged with intact Fontan was 98% (95% CI: 94–99%). The rates of late failure (late death, transplantation, takedown, New York Heart Association class III/IV or protein-losing enteropathy) and adverse events (late failure, reoperation, percutaneous intervention, pacemaker, thromboembolic event or supraventricular tachycardia) per 100 patient-years were 0.8 and 3.8, and their 14-year freedoms were 83% (95% CI: 70–91%) and 53% (95% CI: 41–64%), respectively. After adjustment for confounders, hypoplastic left heart syndrome (HLHS) was strongly associated with prolonged effusions (OR: 2.9, 95% CI: 1.4–5.9), late failure (hazard ratio [HR]: 2.8, 95% CI: 1.1–7.5) and adverse events (HR: 3.6, 95% CI: 1.3–7.5).

CONCLUSIONS: The extracardiac Fontan procedure provides excellent survival into the second decade of life, but half of patients will suffer a late adverse event by 14 years. Patients with HLHS are at higher risk of late adverse events than other morphological groups, but their survival is still excellent.

Keywords: Fontan procedure • Congenital heart disease • Retrospective studies • Survival rate • Follow-up studies • Disease-free survival

† Presented at the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 5–9 October 2013.

INTRODUCTION

Now that the atriopulmonary Fontan [1] has been abandoned, there remain two techniques for Fontan completion: the lateral tunnel [2] and extracardiac conduit (ECC) [3] techniques. No studies to date have definitively shown one technique to be superior to the other [4–10]. Today, patients with palliated hypoplastic left heart syndrome (HLHS) have increasingly survived to Fontan completion and now comprise a larger proportion of patients undergoing Fontan completion, but it is not yet clear how this increase will impact outcomes of the overall Fontan population [11].

In 2008, the Australia and New Zealand Fontan Registry began enrolling all patients in our two countries who have undergone a Fontan procedure [12]. The binational registry has also retrospectively audited perioperative and follow-up information for all patients living with a Fontan procedure in the region. Since 2007, the ECC has become the sole method used to construct total cavopulmonary connections in Australia and New Zealand. In the present analysis, we have focused on analysing early and late outcomes of the subset of patients in the registry who received ECC Fontan procedures at the seven centres in the region, in order to better understand the current expectations of patients operated with this technique.

MATERIALS AND METHODS

The full design, data fields and administration of the Australia and New Zealand Fontan Registry are described elsewhere [12]. Among the 1119 patients whose data were collected in the registry database between 1 January 1975 and 1 January 2013, those who underwent an ECC Fontan procedure prior to 1 January 2010 were identified [13]. Fontan conversions from atriopulmonary connection and Bjork procedures were excluded. During creation of the registry, all Fontan procedures that had been performed were audited retrospectively and this information was entered into the registry database. Patients who consented to participate in the registry have gone on to have their yearly follow-up collected prospectively.

Pre- and perioperative variables were extracted from the database and the recent follow-up data were updated where necessary by contacting the patients' cardiologists and obtaining the latest clinical summary and echocardiogram report. Medical histories were screened for the occurrence of adverse events (defined below), and for the status at the last follow-up, including New York Heart Association (NYHA) class, atrioventricular valve regurgitation, anticoagulation and medications.

Ethical Review Board approvals were obtained at all participating institutions.

Definitions

Hospital mortality was defined as death during the initial hospital stay. Prolonged effusion was defined as effusions requiring pleural drainage for longer than 30 days or requiring reoperation (including pleurodesis). Early failure was defined as death, Fontan takedown, Fontan revision or mechanical support with a ventricular assist device or extracorporeal membrane oxygenation (VAD/ECMO).

Late failure was defined as death, Fontan takedown or transplantation after hospital discharge, protein losing enteropathy/plastic bronchitis (PLE/PB) or NYHA class III/IV at the last follow-up. Late adverse event was defined as late failure, reoperation, transcatheter reintervention (excluding fenestration closure and embolization of aortopulmonary collaterals), recurrent supraventricular tachycardia (SVT), pacemaker insertion, thromboembolic event or atrioventricular valve regurgitation ≥moderate at the last follow-up.

HLHS was defined as left ventricular hypoplasia with aortic stenosis or atresia and/or mitral stenosis or atresia, which precluded biventricular repair.

Concomitant procedures at the time of Fontan were defined by the need for intracardiac procedures excluding atrial septectomy.

Statistical analysis

Values are reported as number (%) for proportions, mean (standard deviation [SD]) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Where appropriate, these data were compared between groups using χ^2 tests, *t*-tests and rank-sum tests, respectively.

Analyses of associations between covariates were performed using logistic regression for early outcomes, and using survival analysis with the Cox proportional hazards method for long-term outcomes, with survival analysis performed as time to first event only.

Multi-level categorical variables were dichotomized if they resulted in models with a better fit. In particular, analysis of morphology, which was originally divided into nine groups with tricuspid atresia as the baseline risk group, was simplified to HLHS versus non-HLHS in most models. For the analysis of adverse events, we divided ventricular morphology into three groups: left ventricle (LV), right ventricle without HLHS (RV non-HLHS) and right ventricle with HLHS (RV HLHS). Exposure variables were chosen for inclusion in multivariable models if they had univariable point estimates of >2.5 or <0.4, or a *P*-value of ≤0.05. Covariates were considered significant in multivariable models if the *P*-value was ≤0.05, or if the *P*-value approached 0.05 and the point estimate was >4 or <0.25. Where collinearity existed between exposure variables, variables were chosen based on clinical relevance for inclusion in multivariable models. Continuous covariates found to have non-linear associations with log-odds and log-hazards were analysed categorically, as was the case for age at the time of the Fontan procedure. Plausibility of the proportional hazards assumption was investigated visually.

Covariates included for analysis are listed in Table 1. Additionally, the occurrence of prolonged effusion was analysed for its effect on late outcomes. We elected not to analyse factors associated with SVT, as the numbers of events were small.

The centre at which the Fontan was performed was included as a categorical variable in the analyses of early outcomes, late failure and late adverse events (Table 2). A binary variable, denoting whether each patient was operated at a high-volume (median ≥10 Fontans/year) or low-volume (median <10 Fontans/year) centre was also included in the analysis.

RESULTS

A total of 570 patients were identified from hospital and surgical databases. Patient characteristics are detailed in Table 1,

Table 1: Patient characteristics, HLHS versus non-HLHS

Characteristics	Non-HLHS (*n* = 490, 86%)[a]	HLHS (*n* = 80, 14%)	Total (*n* = 570)
Male, *n* (%)	283 (58%)	59 (73%)	341 (60%)
Dextrocardia, *n* (%)	46 (9%)	0 (0%)	46 (8%)
Isomerism, *n* (%)	42 (9%)	0 (0%)	42 (7%)
Non-cardiac anomaly, *n* (%)	23 (5%)	1 (1%)	24 (4%)
Ventricular morphology, *n* (%)			
Left	305 (62%)	0 (0%)	305 (54%)
Right	126 (26%)	80 (100%)	206 (36%)
Biventricular/indeterminate	59 (12%)	0 (0%)	59 (10%)
Pre-Fontan procedures			
Number of prior palliations, mean (SD)	2.3 (0.9)	2.8 (1.1)	2.3 (1.0)
Prior aortic arch intervention, *n* (%)	115 (23%)	76 (95%)	191 (34%)
Prior pulmonary artery banding, *n* (%)	149 (30%)	2 (2%)	151 (26%)
Prior staging with BCPS, *n* (%)	470 (96%)	79 (99%)	550 (96%)
Bilateral BCPS, *n* (%)	38 (8%)	6 (8%)	44 (8%)
Age at BCPS in months, median (IQR)	12 (7–19)	4 (3–7)	11 (5–18)
Atrioventricular valve repair/replacement, *n* (%)	29 (6%)	9 (11%)	38 (7%)
Pulmonary artery reconstruction or angioplasty, *n* (%)	100 (20%)	21 (26%)	121 (21%)
Pre-Fontan haemodynamics			
Oxygen saturation (%), mean (SD)	82 (6.4)	81 (6.4)	82 (6.4)
Pulmonary artery pressure (mmHg), mean (SD)	11 (2.7)	11 (2.3)	11 (2.7)
Aortopulmonary or venovenous collaterals, *n* (%)	128 (26%)	17 (21%)	145 (25%)
Arterio-venous malformations, *n* (%)	27 (6%)	4 (5%)	31 (5%)
Atrioventricular valve regurgitation ≥moderate, *n* (%)	35 (7%)	9 (11%)	44 (8%)
Fontan operative characteristics			
Concomitant procedure, *n* (%)	62 (13%)	12 (15%)	74 (13%)
Concomitant pulmonary artery reconstruction, *n* (%)	26 (5%)	6 (8%)	32 (6%)
Concomitant atrioventricular valve repair, *n* (%)	13 (3%)	5 (6%)	18 (3%)
Fenestration, *n* (%)	155 (32%)	64 (80%)	219 (38%)
Age at Fontan in years, median (IQR)	4.8 (3.9–6.1)	4.4 (3.6–5.3)	4.8 (3.9–6.0)

HLHS: hypoplastic left heart syndrome; BCPS: bidirectional cavopulmonary shunt; SD: standard deviation; IQR: interquartile range; mmHG: millimetres of mercury.
[a]Sub-divided into tricuspid atresia (116 patients), double-outlet right ventricle [DORV] (83), complete atrioventricular canal defect (34), complete atrioventricular canal with DORV (26), transposition of the great arteries (29), congenitally corrected transposition of the great arteries (31), double inlet left ventricle (85), pulmonary atresia with intact ventricular septum (51) and other (35).

Table 2: The years of operation, ECC volumes and proportions with HLHS for each centre in the registry

Centre	Number of ECCs/year, median (range)	Number of years of operation	Total number of ECCs performed	Proportion with HLHS, *n* (%)	Proportion with fenestration, *n* (%)
1	13 (8–27)	14	196	53 (27%)	136 (69%)
2	12 (0–18)	14	163	21 (13%)	65 (40%)
3	10 (4–19)	14	151	3 (2%)	8 (5%)
4	2 (0–7)	10	28	0 (0%)	0 (0%)
5	1 (0–6)	11	16	0 (0%)	10 (63%)
6	1.5 (0–10)	4	13	2 (15%)	0 (0%)
7	0 (0–1)	14	3	1 (33%)	0 (0%)

ECC: extracardiac conduit; HLHS: hypoplastic left heart syndrome

comparing HLHS with non-HLHS patients. The volumes of each centre and their respective proportions with HLHS and fenestration are reported in Table 2. The number, proportion and rates of late outcomes are given in Table 3. The results of multivariable analyses for early and late outcomes are presented in Tables 4 and 5, respectively.

Between 1997 and 2006, the lateral tunnel modification was performed alongside the ECC in small numbers, but was completely phased out from 2007. During this period of overlap, we identified from the registry that 78% of patients (385/497 patients) received an ECC (Fig. 1).

Patient and surgical characteristics

The median age at operation was 4.8 years (IQR: 3.9–6.0). Patients with HLHS made up 14% of the cohort (80 patients), and when compared with non-HLHS patients were more likely to be male

Table 3: Prevalences of late outcomes and their incidence rates (95% CIs) of occurrence for hospital survivors with an intact Fontan circulation

Characteristics	Non-HLHS (*n* = 462, 86%)	HLHS (*n* = 78, 14%)	Total (*n* = 540)
Late death			
n (%)	3 (0.6%)	2 (3%)	5 (1%)
Incidence rate (95% CI), per 100 patient-years	0.1 (0.03–0.3)	0.5 (0.1–1.9)	0.1 (0.06–0.3)
Late failure			
n (%)	20 (4%)	7 (9%)	27 (5%)
Incidence rate (95% CI), per 100 patient-years	0.6 (0.4–1.0)	1.7 (0.8–3.7)	0.8 (0.4–1.1)
Thromboembolic events			
n (%)	16 (3%)	2 (3%)	18 (3%)
Incidence rate (95% CI), per 100 patient-years	0.4 (0.3–0.8)	0.5 (0.1–1.9)	0.5 (0.3–0.8)
PLE/plastic bronchitis			
n (%)	7 (2%)	4 (5%)	11 (2%)
Incidence rate (95% CI), per 100 patient-years	0.2 (0.1–0.5)	1.0 (0.4–2.6)	0.3 (0.2–0.6)
Late adverse event			
n (%)	92 (20%)	27 (35%)	119 (22%)
Incidence rate (95% CI), per 100 patient-years	3.3 (2.7–4.0)	7.9 (5.4–11)	3.8 (3.2–4.5)

CI: confidence interval; HLHS: hypoplastic left heart syndrome

Table 4: Results of univariable and multivariable logistic regression for early outcomes

Variable	Univariable		Multivariable		
	OR	95% CI	OR	95% CI	*P*-value
Hospital mortality					
Bilateral BCPS	5.0	0.9–27			
Concomitant procedure	9.8	2.1–45	6.4	1.1–36	0.04
Prolonged effusions	8.3	1.8–38	7.7	1.4–42	0.02
Prior pulmonary artery banding	7.3	1.4–38	10	1.7–62	0.01
Early failure					
Bilateral BCPS	3.0	1.0–9.4			
Prolonged effusions	9.1	3.6–23	8.1	2.8–24	<0.001
Pre-Fontan pulmonary artery pressure in mmHg, per 5 mmHg	2.4	1.1–4.9			
Concomitant procedure	2.8	1.1–7.5			
Age < 3 years	2.8	0.8–10	4.5	0.9–23	0.07
Centre 5 (versus Centre 1)	4.8	1.2–20			
Surgery at a low-volume centre[a]	2.8	1.0–8.0			
Prolonged effusions					
HLHS morphology	3.2	1.7–6.1	2.9	1.4–5.9	0.003
Concomitant procedure	2.3	1.1–4.6	2.1	1.0–4.4	0.04
Pre-Fontan AVMs	2.4	1.0–6.3			
Age at BCPS in months[a]	0.6	0.4–1.0			
Centre 3 (versus Centre 1)	0.4	0.2–0.9			

OR: odds ratio; 95% CI: 95% confidence interval; BCPS: bidirectional cavopulmonary shunt; mmHg: millimetres of mercury; HLHS: hypoplastic left heart syndrome; AVM: arterio-venous malformation.
[a]Omitted from multivariable analysis because of collinearity.

(73 vs 58%, $P = 0.01$) and have undergone a greater number of prior procedures (2.8 ± 1.1 vs 2.3 ± 0.9, $P < 0.001$, Table 1). Fenestration creation was strongly associated with HLHS morphology (80% HLHS vs 32% non-HLHS, $P < 0.001$).

At the time of the Fontan procedure, 73 patients (13%) underwent concomitant procedures, consisting of atrioventricular valve repair in 18 patients, atrioventricular valve closure in 3, atrioventricular valve resection in 1, pulmonary artery reconstruction in 30, pulmonary artery dilatation in 1, anomalous pulmonary venous drainage correction in 3, subaortic resection in 2, Damus–Kaye–Stansel procedure in 4, aortic arch repair in 3, ascending or root aortoplasty in 3, atrial ablation for arrhythmia in 3 and other concomitant procedures in 3.

Centre characteristics

ECC Fontan procedures were performed at one of seven centres (Table 2). Three were designated high-volume centres (median ≥10 Fontans/year), and 4 were low-volume centres (median <10

Table 5: Results of univariable and multivariable Cox proportional hazards analysis for late outcomes

Variable	Univariable		Multivariable		
	HR	95% CI	HR	95% CI	*P*-value
Late death					
HLHS morphology	6.4	1.1–39			
Late failure					
HLHS morphology	3.1	1.3–7.4	2.8	1.1–7.5	0.04
Fenestration	2.5	1.2–5.4			
Common AV valve	2.5	1.0–6.3	3.8	1.4–10.1	0.01
Centre 3 (versus Centre 1)	0.2	0.04–0.8			
Late thromboembolic events					
Pre-Fontan pulmonary artery pressure in mmHg, per 5 mmHg	2.4	1.1–5.5	2.4	1.1–5.5	0.03
Pre-Fontan pulmonary artery band	2.6	1.0–6.7			
Late PLE					
HLHS morphology	4.8	1.4–16.8			
Right ventricular morphology	9.0	1.9–42	6.9	1.3–36	0.02
Pre-Fontan AV valve regurgitation ≥moderate	6.2	1.6–24			
Pre-Fontan aortic arch intervention[a]	6.0	1.6–23			
Postoperative effusions	4.2	1.1–16			
Late adverse events					
Morphology					
TA	Reference group	Reference group			
HLHS	4.5	2.3–8.9	3.6	1.3–7.5	0.001
DORV	2.9	1.4–5.8	2.6	1.3–5.4	0.008
CAVC	3.1	1.4–7.0	2.9	1.3–6.6	0.01
CAVC-DORV	4.2	1.8–10.1	3.2	1.2–8.3	0.02
Fenestration	1.7	1.2–2.5			
Prolonged postoperative effusions	1.8	1.0–3.2			
Pre-Fontan haemodynamics					
Oxygen saturation (per 5%)	0.8	0.7–0.9	0.8	0.7–1.0	0.04
≥Moderate AV valve regurgitation	2.4	1.4–4.1			
Arterio-venous malformations	2.3	1.3–4.2			
Centre					
Centre 1	Reference group				
Centre 3	0.3	0.2–0.6			
Centre 4	0.2	0.1–0.9			

HR: hazard ratio; 95% CI: 95% confidence interval; HLHS: hypoplastic left heart syndrome; AV: atrioventricular; mmHg: millimetres of mercury; TA: tricuspid atresia; DORV: double outlet right ventricle; CAVC: complete atrioventricular canal; TGA: transposition of the great arteries; ccTGA: congenitally corrected transposition of the great arteries; PA-IVS: pulmonary atresia with intact ventricular septum; CAVC-DORV: complete atrioventricular canal with double outlet right ventricle.
[a]Variables not entered into multivariable analysis due to causal relationship with HLHS morphology.

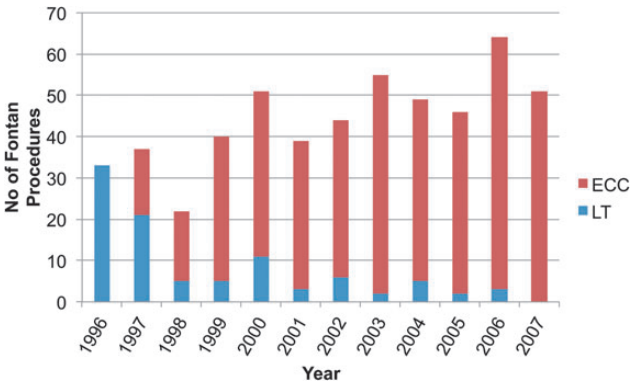

Figure 1: The number of extracardiac conduit (ECC) and lateral tunnel (LT) Fontan procedures performed during the period of overlap from 1997 to 2006, where both techniques were used concurrently in Australia and New Zealand. The LT was rapidly phased out so that the ECC constituted 78% (385/497 patients) of procedures during this period. From 2007 onwards, the ECC was the sold technique used.

Fontans/year). Centres 1–3 and 7 were operational throughout the entire study period. The caseload of Centres 1 and 2 incorporated a higher proportion with HLHS compared with the third high-volume centre. By multivariable analysis, neither centre nor centre volume were associated with any differences in early or late outcomes.

Early outcomes

There were 7 hospital mortalities (1.2%). No death occurred out of hospital within the first 30 days after surgery. One patient died on postoperative day 2 after an embolic stroke. Two patients had Fontan takedowns for low cardiac output syndrome with prolonged effusions prior to death on days 79 and 80. Another 3 patients suffered low output syndrome and died despite ECMO support in 2 and Fontan circuit revision in 1, on days 23, 73 and 81, respectively. The final patient, who underwent a concomitant Damus–Kaye–Stansel procedure, died on postoperative day 4, after myocardial infarction caused by a narrowed right coronary ostium. A further 6 patients underwent Fontan takedown during the initial hospital stay, because of prolonged effusions in 4 patients and low cardiac output syndrome in 2. By multivariable analysis, factors associated with hospital mortality were concomitant procedure at the time of Fontan, prolonged effusions and

prior pulmonary artery banding (ORs [95% CIs]: 6.4 [1.1–36], 7.7 [1.4–42], 10 [1.7–62], respectively).

The median length of hospital stay was 12 days (IQR: 9–17 days). Prolonged effusions occurred in 51 patients (9%), of whom 22 (43%) underwent reoperation, and resulted in an increase in the median length of stay to 41 days (IQR: 31–53). Length of stay >30 days occurred in 57 patients (10%), and was due to prolonged effusions in 39 patients, cerebral infarction in 5 patients, persistent low output syndrome in 4 patients, wound infection and renal failure in 1 and unspecified causes in 9. Four patients required mechanical circulatory support (3 with ECMO, 1 with VAD), and associated mortality was 50% (2 patients). Early failure (death, takedown, revision or VAD/ECMO) occurred in 21 patients (4%). The factors associated with prolonged effusions were HLHS and concomitant procedure at the time of Fontan (OR [95% CI]: 2.93 [1.4–6.9] and 2.1 [1.0–4.4], respectively). Factors associated with early Fontan failure were prolonged effusions (OR: 8.1, 95% CI: 2.8–24) and age < 3 years at Fontan (OR: 4.5, 95% CI: 0.9–23).

Perioperative clinical cerebral infarction occurred in 10 patients (2%). These consisted of embolic stroke in 4 patients, watershed infarcts secondary to low output state in 3 and intraoperative anoxic cerebral injury in 3. The median length of stay was prolonged to 37 (IQR: 27–60) days, and mortality after perioperative cerebral infarction was 10% (1 patient).

Follow-up

After excluding patients referred and followed internationally (17 patients), those who had Fontan takedown during the initial hospital stay (6 patients), and hospital mortalities (7 patients), 540 patients remained for survival analysis. Late follow-up was available in 529 patients (98%), and 11 (2%) were lost to follow-up. Survival analysis was undertaken on 3565 patient-years of follow-up. Follow-up beyond 10 years was available in 107 patients (20%), and mean follow-up was 6.7 years (SD: 3.5). Mean follow-up among HLHS patients was significantly shorter, at 5.3 years (SD: 3.1, $P < 0.001$).

Survival

Actuarial survival at 14 years was 96% (95% CI: 93–98%). Late survival of patients discharged alive with an intact Fontan circulation (540 patients) was 98% (95% CI: 94–99%) at 14 years. There were 5 late deaths, 2 among patients with HLHS and 3 among the others. These were due to sudden death in 1 patient, drowning in 1, plastic bronchitis in 1 and acute-on-chronic right ventricular failure in 1. The final patient, who had borderline ventricular function at the time of Fontan completion, underwent transplantation 3 months later for worsening biventricular function and was retransplanted 5 years later, after developing accelerated graft atherosclerosis. He finally died after failed reoperation for a mycotic ascending aortic aneurysm. The only factor associated with late death was HLHS (HR: 6.4, 95% CI: 1.1–39).

Late failure and reintervention

Late failure occurred in 27 hospital survivors (5%), consisting of 4 late deaths, 9 transplants, 1 late takedown and 12 patients who were in NYHA class 3 at the last follow-up. Fourteen-year freedom from late failure was 83% (95% CI: 70–91%). Factors associated with late failure were HLHS (HR: 2.8, 95% CI: 1.1–7.5) and common atrioventricular valve (HR: 3.8, 95% CI: 1.4–10). Patients operated on at Centre 3 exhibited a trend towards lower risk of late failure; however, this was not statistically significant in the multivariable model after adjustment for morphological differences.

Major reoperations occurred in 24 patients, consisting of Fontan circuit revision in 5 patients, atrioventricular valve repair in 5, atrioventricular valve replacement in 2, Damus–Kaye–Stansel procedure in 2, aortic arch reconstruction in 1, aortic root replacement (Bentall's procedure) in 1, aortic root reconstruction in 2, pulmonary artery reconstruction in 1 and other in 4. Transcatheter intervention occurred in 25 patients (5%), pulmonary artery angioplasty ± stent in 18, radiofrequency arrhythmia ablation in 3, aortic balloon dilatation in 2, Fontan fenestration with stent in 1 and Fontan stent in 1. Patients from Centre 2 experienced the majority of transcatheter pulmonary artery interventions (17 patients from Centre 2 versus 1 from Centre 1). The fenestration was closed in 52 of the 210 patients (25%) who had a primary fenestration, and 2 more who underwent fenestration during the early postoperative period as part of a Fontan revision. Centre 2 performed 80% of fenestration closures (43/54 patients). Freedom from reintervention at 5, 10 and 14 years was 91% (95% CI: 87–93%), 83% (78–87%) and 75% (64–83%), respectively (Fig. 2).

Arrhythmia and thromboembolic events

Pacemakers were implanted in 29 patients (5%). Pacemakers were already present in 8 patients at the time of the Fontan procedure. Implantation occurred at the time of Fontan in 5 patients, during the early hospital stay in 15 and during long-term follow-up in 9. Actuarial requirement for pacemaker at 14 years was 6% (95% CI: 4–9%) overall and 2% (95% CI: 1–5%) during the late follow-up. Six patients developed SVT, and 14-year freedom from SVT was 98% (95% CI: 94–99%). Four of the 6 patients with SVT had isomerism, and all patients had undergone Fontan completion after 5 years of age.

Symptomatic thromboembolism occurred in 8 patients at late follow-up. These included 2 strokes, 3 transient ischaemic attacks and 3 pulmonary emboli. A further 10 patients had thrombus detected within the conduit on routine echocardiography during

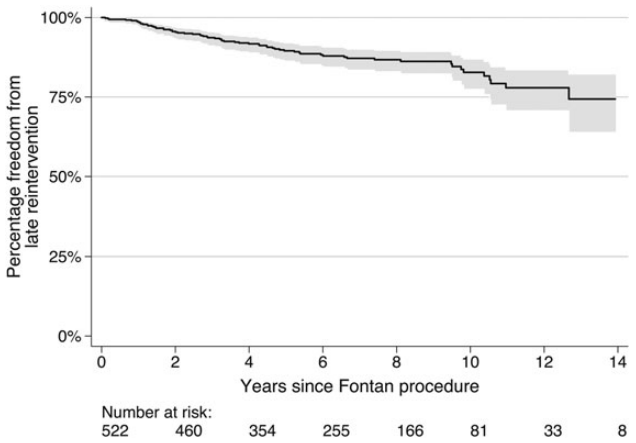

Figure 2: Freedom from late reintervention (surgical reoperation or transcatheter intervention excluding fenestration closure and embolization of aortopulmonary collaterals).

follow-up. The incidence rate of thromboembolic events was 0.5 (95% CI: 0.3–0.8) per 100 patient-years follow-up, and freedom from thromboembolic events was 91% (95% CI: 77–97%) at 14 years.

Late adverse events

Late adverse events (death, failure, transplantation, reoperation, catheter reintervention [excluding fenestration closure and embolization of aortopulmonary collaterals], thromboembolic event, arrhythmia or pacemaker) occurred in 119 patients (22%), at an incidence rate of 7.9 per 100 patient-years (95% CI: 5.4–11) for HLHS vs 3.3 (95% CI: 2.7–4.0) for non-HLHS patients (Table 3, Fig. 3). In unadjusted models, rates of adverse events between LV, RV non-HLHS and RV HLHS were significantly different (2.8 [95% CI: 2.2–3.6] vs 4.7 [95% CI: 3.3–6.6, $P = 0.02$] vs 7.9 [95% CI: 5.4–11.5, $P < 0.001$]).

Event-free late survival for all patients at 5, 10 and 14 years was 84% (95% CI: 80–87%), 70% (64–75%) and 53% (41–64%). By multivariable analysis, factors associated with late adverse events were HLHS (HR: 3.6, 95% CI: 1.3–7.5), double outlet right ventricle (DORV) (HR: 2.6, 95% CI: 1.3–5.4), complete atrioventricular canal ± DORV (HR: 2.9, 95% CI: 1.3–6.6 and HR: 3.2, 95% CI: 1.2–8.3, respectively) and lower pre-Fontan oxygen saturation (HR: 0.8 for every 5% increase, 95% CI: 0.7–1.0).

ACE inhibitors and anticoagulation

At last follow-up, 185 patients (35%) were on angiotensin converting enzyme inhibitors. By multivariable logistic regression, factors associated with angiotensin converting enzyme inhibitors, use were HLHS, complete atrioventricular canal (CAVC) and fenestration (adjusted ORs [95% CIs]: 3.1 [1.6–6.3], 3.1 [1.4–7.1] and 1.8 [1.3–2.8], respectively).

Anticoagulation at last follow-up was with warfarin in 303 patients (56%), aspirin in 167 (31%) and a combination in 9 (2%). No anticoagulation was used in 34 patients (6%), and anticoagulation information was not available in 27 (5%). After correction for morphology, fenestration was strongly associated with the use of warfarin (adjusted OR: 5.0, 95% CI: 3.1–7.9).

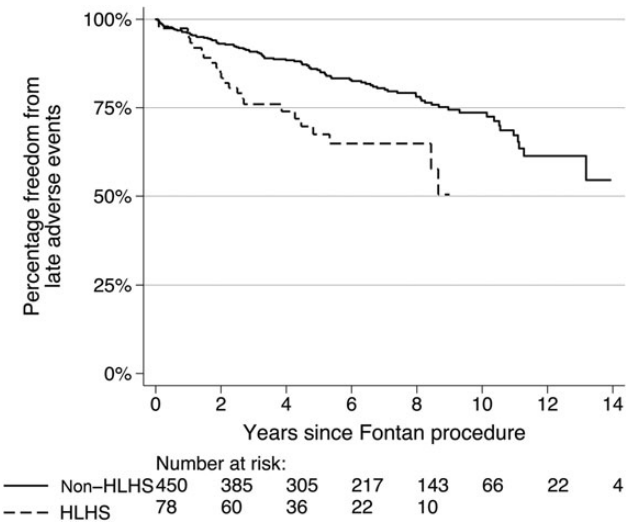

Figure 3: Freedom from late adverse events (death, failure, transplantation, reoperation, catheter reintervention excluding fenestration closure and embolization of aortopulmonary, thromboembolic event or arrhythmia). Log-rank *P*-value < 0.001.

DISCUSSION

In the 40 years since the introduction of the Fontan procedure, significant gains have been made in the care of patients born with a single ventricle. Results have improved to the point that now, after the ECC Fontan procedure in Australia and New Zealand, hospital mortality is only 1 and 96% of patients overall can expect to survive beyond adolescence and into early adulthood. This series comprised a large group of contemporaneous patients undergoing homogenous surgical techniques from a single era. While outcomes for HLHS are worse compared with other anatomical subgroups, they are not as bad after the Fontan in our experience as previously reported [11]. Late mortality, while statistically worse, comprised a very small number of patients (3 non-HLHS versus 2 HLHS) and we are encouraged that, with 14 years of follow-up, these worse outcomes do not yet translate into major differences in mortality.

Adverse events

For every 25 years of survival with a Fontan circulation, one adverse event will occur. In our estimate, with time all patients will require some kind of reintervention or experience an adverse event (Fig. 3). While HLHS emerged as a recurrent factor associated with poorer outcomes, the presence of a common atrioventricular valve or right ventricular-dominant morphology (DORV and CAVC-DORV) was also associated with late failure and adverse events.

It has been our experience that common atrioventricular valves are prone to developing late regurgitation, which is poorly tolerated in the univentricular circulation [14]. It is possible that we can further improve how we deal with this challenging subset of patients, by careful timing of pre-Fontan atrioventricular valve repair and close surveillance for signs of valve regurgitation with associated ventricular dysfunction [15].

This series of 529 patients followed up for a total of 3565 patient-years also demonstrates that with the ECC the incidence of supraventricular tachycardia and pacemakers is low, as others had predicted it would be [6, 16]. The 98% freedom from supraventricular arrhythmia and the low rate of late pacemakers appear better than in other series, especially those describing the lateral tunnel modification, in which the quoted occurrence of SVT during late follow-up is 5–25% [4, 5, 8]. Most notably, in all series the main indication for pacing after the ECC is sinus node dysfunction as opposed to heart block.

Early outcomes

In the current era, a focus must still remain on improving in-hospital morbidity. Length of stay beyond 30 days still occurs in 1 in 10 patients, and significant morbidity from prolonged effusions and perioperative strokes remains. Prolonged effusions were associated with both early failure and hospital mortality, but did not impact on long-term outcomes. In Australia and New Zealand, the typical practice is to complete the Fontan at between 3 and 6 years of age.

The disadvantage of completing the Fontan earlier than 3 years was demonstrated here for early Fontan failure.

Variation in outcomes and treatment practices between centres

The present series demonstrates relatively similar outcomes across the centres in the region, after correction for the marked differences in treatment practice and patients' characteristics. The ECC can be performed with similarly good outcomes at high- and low-volume centres in our experience. Due to regional policies, 2 of the 3 high-volume centres dealt with 93% of the patients with HLHS (74/80 patients), and by multivariable analysis these centres' outcomes were not worse. Fontan fenestration, which was previously demonstrated in a randomized trial to protect against postoperative effusions [17], did not display a similar effect in this series. There was variation between centres in the practice of fenestration, which can be partly explained by the differences in the proportion with HLHS. The centre with the largest volume of HLHS routinely includes a fenestration in the absence of veno-venous collaterals while others selectively fenestrate only high-risk groups such as those with HLHS. These data thus support the argument that, in the current era, selective fenestration may achieve results similar to those obtained in routine fenestration for patients who do not have HLHS [18, 19]. The variable incidence of post-Fontan transcatheter pulmonary artery intervention between centres probably reflects differing philosophies of post-Fontan management. Whether a proactive interventional stance will improve long-term outcomes remains to be seen.

Long-term surveillance

Adverse events continue to occur into the second decade after the Fontan procedure. This crucial time frame, when patients transition from paediatric cardiology care to adult congenital follow-up, is when they are most at risk of becoming lost to follow-up [20]. Moving forward, in order to achieve improvements in late outcomes, we in line with others [21] emphasize the importance of successful transition to adult care and ongoing surveillance into adulthood. With the emergence of chronic liver disease secondary to systemic venous hypertension as a common phenomenon into the second and third decade [22, 23], the true longevity of adults with a Fontan of any type remains in question. It would thus be inappropriate for patients to perceive a 'laissez faire' attitude to the follow-up. We must now emphasize to patients the near-certainty that they will develop a serious complication or require further intervention. The patients in this series were not yet old enough to demonstrate attrition from follow-up, and we are optimistic that the registry will prevent them from suffering the same fate as we have seen in hundreds of patients with the older atriopulmonary and lateral tunnel Fontan connections, who are frequently no longer regularly seen for surveillance in our region [12].

Limitations

The inherent limitations of retrospective series are well known. Registry data are limited by the inability to analyse retrospectively for factors that may cluster together (e.g. fenestration and HLHS); analysis of the benefits of interventions such as fenestration in Fontan circuits ideally require randomized controlled trials with long-term follow-up; however, such studies are logistically difficult in relatively rare conditions and such data are currently unavailable for single-ventricle patients. While these data come from a population-based registry of Fontan patients, our analysis does not take into account the true denominator of all children born with univentricular cardiac defects who do not survive to Fontan completion, and hence, this analysis does not control for selection bias. The subset of patients having an ECC were not the entire population offered Fontan surgery between 1997 and 2006, but they represent the majority (~80%). The definition chosen for the coding of prolonged effusions in our database is beyond the threshold most clinicians would define as 'prolonged', and this is because we sought to isolate the truly troublesome effusions. While we performed univariable analysis for factors associated with late death, the number of events was small, limiting the accuracy of this analysis. An analysis of longitudinal treatment practices and their effect on outcomes is currently underway. It is likely that a number of correlations observed, such as those between ACEI, warfarin and fenestration, are also the result of regional practice variations.

CONCLUSION

In conclusion, results of the ECC in Australia and New Zealand are excellent, with low rates of death, thromboembolism and arrhythmia. However, half of patients will suffer an adverse event by 14 years. Patients with HLHS are more prone to poor outcomes across the board, but their survival is not affected at this stage.

ACKNOWLEDGEMENTS

The authors thank our research assistants, Ingrid King, Aneta Kotevski, Janina Chapman, Gabriela Abrahamson, Megan Upjohn and Lisa Cowcher for their invaluable assistance in the creation and maintenance of the registry. The authors acknowledge support provided to the Murdoch Childrens Research Institute by the Victorian Government's Operational Infrastructure Support Program.

Funding

The Australia and New Zealand Fontan Registry is funded by grants from the NHMRC (APP1012241) Heart Kids and the ANZ Bank Trustees. Ajay J. Iyengar has received postgraduate awards from the Royal Australasian College of Surgeons (Catherine Marie Enright Kelly and Eric Bishop Scholarships) and the National Health and Medical Research Council (NHMRC) and the National Heart Foundation of Australia (APP1038802). Yves d'Udekem is a Career Develop-ment Fellow of the National Heart Foundation of Australia (CR 10M 5339).

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr R. Ohye *(Ann Arbor, MI, USA)*: Kudos to your two countries for putting together this registry. This type of collaboration is the only way I think that we're going to solve a lot of the questions in congenital heart disease. I have three relatively simple questions.

I notice that you have a fairly high incidence of prolonged pleural effusions. In our series of about 600 patients over 15 years, we had an interesting finding of a relationship between pleural effusions and late development of PLE, and I was wondering if you had noted that.

Dr Iyengar: No. I did study prolonged pleural effusions as a risk factor for late outcomes, and in some univariate analyses, it did come out. But after correction for other things like hypoplastic left heart syndrome, it appears that it's other factors that are driving the late outcomes rather than prolonged effusions.

Dr Ohye: My second question relates to one of your slides that said there was a fair amount of centre variation. Did you control for centre when you did your multivariable analysis because obviously things like, as you mentioned, fenestration may have a profound impact on morbidity and mortality.

Dr Iyengar: Because practices were associated with centre, if you control for both in a multivariable analysis, it throws the model off. So we didn't specifically correct for centres in this analysis, but it is something that I'm looking at performing later on perhaps with the whole cohort of all the Fontans to see what effect centre has.

Dr Ohye: And then lastly, you have excellent results, but do we know anything about the true denominator of the group, how many patients presented either at the very beginning of their pathway through single ventricle repair? Obviously if you front load your mortality early on, it's going to affect your late results. Or do you have any information on the number of patients at Stage II that were or were not candidates? For instance, you had the slide about good and bad candidates for a Fontan. Not to criticize that you have slanted results, but it's also important for us to understand who are good candidates, who should not go on to a Fontan, who could be better off as a Glenn, plus or minus a shunt, in the future, or a transplant. Do you have any data that will help us to understand who should or should not to go on to a Fontan?

Dr Iyengar: Look, I think part of what's driving the improvement in results with time when you compare it to the era of the atrio-pulmonary Fontan is that we've improved our patient selection now. So we're not operating on really borderline Fontan candidates. In terms of getting the true denominator, we've previously published a series of all single-ventricle patients, and that was that slide that I presented that showed the main driver was right ventricular morphology before the Fontan. But aside from creating a registry of all univentricular hearts, unfortunately, I don't have that information for you right now.

Dr S. Sano *(Okayama, Japan)*: I think the mortality after Fontan mostly depends on the preoperative risk factors or the conditions. If you choose a good Fontan patient, then I think the mortality is very low; if you do the high-risk patient, the mortality is higher. Do you have any preoperative data on the hypoplastic group and LV dominant group? Is there any difference?

Dr Iyengar: The main characteristics that were different in the hypoplastic left heart syndrome patients are the factors that I showed. They were more likely to be fenestrated because they were considered borderline candidates and because they were operated on in centres where fenestration was the rule generally. Also, they were more likely to be male. They didn't differ in their pulmonary artery pressure. They didn't differ in their incidence of atrioventricular valve regurgitation.

We didn't study left ventricular or single-ventricle end-diastolic pressure, but the ones that came forward to Fontan generally had similar characteristics.

Dr Sano: I also think the right ventricle dominant patient is worse than the left ventricle dominant patient; therefore, we started progenitor cell therapy for these patients. And I think the response is very good, especially in the small children.

Dr D. Anderson *(London, UK)*: Can I ask, is it possible that your worse outcomes relating to hypoplastic left heart is simply a reflection of the further back you go in your series? Obviously your early days of hypoplastic left heart surgery, and I think we've all learned a good deal about how to do the operation and how to get a better outcome, would reflect more the learning curve of your HLH surgery rather than the outcomes of the eventual Fontan?

Dr Y. d'Udekem, *Victoria, Australia*: I think that you're probably right in the fact that outcomes today are better. But it's always very surprising to notice that we always believe we are doing better than before, but more and more by doing these follow-up studies, I realize that you have to prove it. So maybe we are doing better, but at the present time that's the standard. And before we prove that we are doing better, that should be our reality.