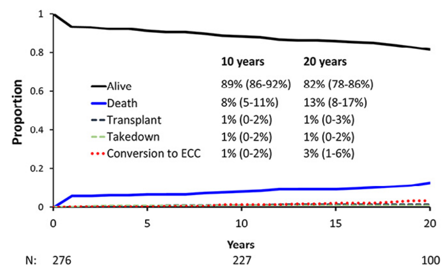
Twenty-Five Year Outcomes of the Lateral Tunnel Fontan Procedure

Thomas G. Wilson, BSc, MD,[*,†,‡] *William Y. Shi, MBBS,*[*,†,‡]
Ajay J. Iyengar, MBBS (Hons), BMedSci, PhD,[*,†,‡]
David S. Winlaw, MBBS (Hons), MD, FRACS,[§,||] *Rachael L. Cordina, MBBS, FRACP,*[||,¶]
Gavin R. Wheaton, MBBS, FRACP,[#] *Andrew Bullock, MBBS, FRACP,*[**]
Thomas L. Gentles, MBChB, FRACP,[††] *Robert G. Weintraub, MBBS, FRACP,*[†,‡‡]
Robert N. Justo, MBBS, FRACP,[§§] *Leeanne E. Grigg, MBBS, FRACP,*[||||]
Dorothy J. Radford, MBBS, MD, FRACP,[¶¶,##] *Yves d'Udekem, MD, PhD,*[*,†,‡] *and The Australia and New Zealand Fontan Registry*

The objective of this study was to characterize late outcomes of the lateral tunnel (LT) Fontan procedure. The outcomes of all patients who underwent an LT Fontan procedure in Australia and in New Zealand were analyzed. Original files were reviewed and outcomes data were obtained through a binational registry. Between 1980 and 2014, a total of 301 patients underwent an LT Fontan procedure across 6 major centers. There were 13 hospital mortalities, 21 late deaths, 8 Fontan conversions and revisions, 8 Fontan takedowns, and 4 heart transplantations. Overall survival at 15 and 25 years was 90% (95% confidence interval [CI]: 86%-93%) and 80% (95% CI: 69%-91%), respectively. Protein-losing enteropathy or plastic bronchitis was observed in 14 patients (5%). Freedom from late failure at 15 and 25 years was 88% (95% CI: 84%-92%) and 82% (95% CI: 76%-87%), respectively. Independent predictors of late Fontan failure were prolonged pleural effusions post Fontan



Competing events' cumulative incidence curves for all patients (N = 301).

Central Message

Late survival after the lateral tunnel Fontan procedure is excellent. This population is subjected to an ongoing risk of late failure.

Perspective Statement

Late survival after the lateral tunnel Fontan procedure is excellent. There is, however, an ongoing risk of failure of the Fontan circulation in this population. The onset of new arrhythmia predicts later occurrence of failure, and it is likely that careful monitoring of this population is warranted as their atrial channel might be subjected to progressive dilatation.

*Department of Cardiac Surgery, Royal Children's Hospital, Melbourne, Victoria, Australia
†Heart Research Group, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia
‡Department of Paediatrics, Faculty of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
§The Heart Centre for Children, The Children's Hospital at Westmead, Sydney, New South Wales, Australia
||Department of Paediatrics, University of Sydney, Sydney, New South Wales, Australia
¶Department of Cardiology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
#Department of Cardiology, Women's and Children's Hospital, Adelaide, South Australia, Australia
**Children's Cardiac Centre, Princess Margaret Hospital for Children, Perth, Western Australia, Australia
††Greenlane Paediatric and Congenital Cardiac Service, Starship Children's Hospital, Auckland, New Zealand
‡‡Department of Cardiology, Royal Children's Hospital, Melbourne, Victoria, Australia
§§Queensland Paediatric Cardiac Service, Lady Cilento Children's Hospital, Brisbane, Queensland, Australia
||||Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia
¶¶Adult Congenital Heart Unit, The Prince Charles Hospital, Brisbane, Queensland, Australia
##Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia

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Address reprint requests to Yves d'Udekem, MD, PhD, Department of Cardiac Surgery, Royal Children's Hospital, Flemington Rd, Parkville, Vic. 3052, Australia. E-mail: yves.dudekem@rch.org.au

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operations (hazard ratio [HR] 3.06, 1.05-8.95, $P = 0.041$), age >7 years at Fontan (vs 3-5 years, HR 9.7, 2.46-38.21, $P = 0.001$) and development of supraventricular tachycardia (HR 4.67, 2.07-10.58, $P < 0.001$). Freedom from tachy- or bradyarrhythmias at 10 and 20 years was 87% (95% CI: 83%-91%) and 72% (95% CI: 66%-79%), respectively. Thromboembolic events occurred in 45 patients (16%, 26 strokes), and freedom from symptomatic thromboembolism at 10 and 20 years was 93% (95% CI: 89%-96%) and 80% (95% CI: 74%-86%), respectively. Over a 25-year period, the LT technique has achieved excellent late survival. As this population ages, it is at an increasing risk of failure and adverse events. We are likely to see an increasing proportion requiring heart transplantation and late reintervention.

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INTRODUCTION

The efficacy of the Fontan procedure in the treatment of children born with single-ventricle cardiac malformations continues to be unveiled as this population progresses further into adulthood.[1] It is believed that refinements in surgical techniques have led to an improvement in outcomes since the original atriopulmonary (AP) Fontan, which has now been abandoned.[2,3] Progressive atrial distension and the development of turbulent flow within the atrial chamber predisposed recipients to tachyarrhythmias, thromboembolic events, and even compression of the pulmonary veins.[4] In 1988, the concept of total cavopulmonary circulation was proposed by de Leval in an attempt to avoid turbulent flow within the atrium, and his design of the intra-atrial lateral tunnel (LT) Fontan was widely adopted.[5] In the 1990s, the extracardiac conduit (ECC) progressively came into vogue and today is the most frequently performed type of Fontan.[6,7] Many patients have undergone an LT Fontan operation and the specific outcomes of this form of Fontan are unclear. In 1 U.S. multicenter database, more than a third of the Fontan operations performed between 2000 and 2009 were undertaken using the LT technique.[7] Locally, a quarter of the patients with a Fontan circulation currently followed up within our region are living with an LT Fontan type.[1,8] Although the implementation of this technique has resulted in improved survival up to early adulthood, the rate of failure of their circulation is still unclear. We sought to characterize the late outcomes of the patients who have undergone an LT Fontan procedure in Australia and in New Zealand.

METHODS

Ethical review board approvals were obtained at all participating institutions. The need for specific consent was waived because of the retrospective nature of the study.

The full design, data fields, and administration of the Australia and New Zealand Fontan Registry have been described previously.[1,8] Of the 1462 participants whose data were collected in the Registry database between January 1, 1975, and August 1, 2015, all those who underwent an LT Fontan were identified. Fontan conversions from AP connection and Bjork procedures were excluded.

Perioperative variables were extracted from the database and follow-up data were updated where necessary by contacting the patients' cardiologists and obtaining their latest clinical summaries and echocardiogram reports. Medical histories were screened for missing data.

The LT technique was gradually phased out between 1997 and 2006 because of the potential theoretical advantages of the ECC, whereafter the ECC modification was solely performed throughout the region. Over this time period, the decision to fenestrate the Fontan was left to surgical preference.

Definitions

Hospital mortality was defined as death during the initial hospital stay. *Prolonged pleural effusion* was defined as effusions requiring pleural drainage persisting for more than 30 days or requiring reoperation including pleurodesis. *Early failure* was defined as death, a Fontan takedown, a Fontan revision, or mechanical support with a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO) within 30 days or during the initial hospital stay. *Late failure* was defined as death, a Fontan takedown, or a conversion to ECC after hospital discharge, heart transplantation, protein-losing enteropathy, plastic bronchitis, or New York Heart Association (NYHA) Class III or IV. *Concomitant procedures* were defined as intracardiac procedures performed at the time of the Fontan operation, excluding atrial septectomy.

Analyses of long-term outcomes were performed only on those who were discharged from the hospital with an intact Fontan circulation (ie, excluding Fontan takedowns performed during the same admission as their initial operation).

Statistical Analysis

Values were reported as absolute value (percentage [%]) for proportions, mean (standard deviation) 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 Wilcoxon rank-sum tests, respectively.

Multivariable logistic regression was used to identify independent predictors of early outcomes, and Cox regression was utilized to identify predictors of early and late outcomes. The backward elimination method was used in regression analyses to include all potential predictors of end points in the initial models and subsequently eliminate covariates in an iterative process to create a final model. Variables with at least moderate evidence against the null hypothesis ($P < .10$) were included. Inclusion of all potentially important variables in the initial model allows their joint predictive behavior to be initially evaluated, which is important, given that a set of variables may exhibit predictive capability even if a subset does not. The variables used in regression analyses were selected based on those found to be associated with outcomes in prior studies by our group as well as based on our group's clinical experience. Because of the nonlinear relationship of age at the time of Fontan with the risk of late outcomes, the patients were grouped into categories based on their age at Fontan: <3 years, 3-5 years, 5-7 years, and >7 years, with 3-5 years as the reference group. Similarly, oxygen saturation before the Fontan procedure was divided into the following categories: <77%, 78%-81%, 82%-85%, and >86%, and comparisons were made using the 82%-85% category as the reference group. Linearity was examined by performing a likelihood ratio test comparing regression models with continuous covariates against models in which the numeric variable had been categorically transformed. The age at the Fontan operation had nonlinear associations with mortality and the other end points, and was analyzed as a categoric variable.

The time of the first onset of an arrhythmia was inserted into the multivariable Cox regression model as a time-varying covariate and its associated hazard ratio (HR) was calculated. In essence, patient follow-up was split into 2 periods: before and after the onset of arrhythmia, allowing the association between the development of an arrhythmia and subsequent late end points to be established. Analysis of long-term outcomes where the onset of supraventricular tachycardia (SVT) was used as a covariate occurred only in those who were discharged with an intact Fontan circulation. As such, the onset of SVT and its association with early failure was not studied.

The estimated cumulative incidence curves for each competing event post Fontan (being discharged alive, death, transplant, takedown, and conversion to ECC) were constructed using the cumulative incidence function described by Scrucca et al.[9] Here, the cumulative incidence function is defined as the probability of failing from cause r ($r = 1, \ldots, k$, where k is the number of causes of failure) up to a certain time point t, such that

$$I_r(t) = \Pr(T \leqslant t, R = r) = \int_0^t \lambda_r(u) S(u) \mathrm{d}u \quad \text{for } r = 1, \ldots, k$$

where $\lambda r(t)$ is the cause-specific hazard rate and $S(t) = \Pr(T \geq t)$ is the survival function. The nonparametric maximum likelihood estimation of (cause-specific) cumulative incidence is

$$\hat{I}_r(t) = \sum_{j: t_j \leqslant t} \frac{d_{rj}}{n_j} \hat{S}(t_{j-1}) \quad \text{for } r = 1, \ldots, k.$$

RESULTS

A total of 301 patients were identified from hospital and surgical databases. Patient characteristics are detailed in Table 1.

Patient and Surgical Characteristics

At the time of the Fontan operation, 71 patients (24%) underwent concomitant procedures, consisting of pulmonary artery reconstruction in 21 patients, Damus-Kaye-Stansel procedure in 8, atrioventricular valve repair in 9, subaortic resection in 8, semilunar valve repair in 4, ventricular septal defect enlargement in 5, pulmonary artery band revision in 4, main pulmonary artery ligation or division in 5, aortic arch reconstruction in 2, arterial switch

Table 1. Patient Characteristics

Characteristics	Total (N = 301)
Male, n (%)	165 (55)
Anatomical comorbidities, n (%)	
Dextrocardia or mesocardia	24 (8)
Isomerism or heterotaxy	21 (7)
Noncardiac anomaly	42 (14)
Ventricular morphology, n (%)	
Left	188 (63)
Right	81 (27)
Biventricular or indeterminate	32 (11)
Primary morphological diagnosis, n (%)	
TA	81 (27)
DILV	65 (22)
DORV	50 (17)
CAVC	28 (9)
PA-IVS	19 (6)
ccTGA	18 (6)
TGA	12 (4)
HLHS	9 (3)
PA-VSD	6 (2)
Other	13 (4)
Pre-Fontan procedures	
Number of prior palliations, mean (SD)	2 (1)
Prior aortic arch intervention, n (%)	39 (13)
Prior pulmonary artery banding, n (%)	90 (30)
Prior staging with BCPS, n (%)	120 (40)
Bilateral BCPS, n (%)	7 (2)
Age at BCPS, median (IQR), y	1.4 (0.8-2.8)
Atrioventricular valve repair or replacement, n (%)	7 (2)
Pulmonary artery reconstruction or angioplasty, n (%)	35 (12)
Pre-Fontan hemodynamics	
Oxygen saturation (%), mean (SD)	81 (7)
Pulmonary artery pressure (mm Hg), mean (SD)	12 (4)
Aortopulmonary or venovenous collaterals, n (%)	25 (8)
Atriovenous malformations, n (%)	7 (2)
Atrioventricular valve regurgitation ≥moderate, n (%)	12 (4)
Fontan operative characteristics	
Age at Fontan, median (IQR), y	3.8 (2.8-5.9)
Concomitant procedure, n (%)	77 (26)
Concomitant pulmonary artery reconstruction, n (%)	20 (6)
Concomitant atrioventricular valve repair or replacement, n (%)	8 (3)
Fenestration, n (%)	156 (52)

BCPS, bidirectional cavopulmonary shunt; CAVC, common atrioventricular canal; ccTGA, congenitally corrected transposition of the great arteries; DILV, double-inlet left ventricle; DORV, double-outlet right ventricle; PA-IVS, pulmonary atresia with intact ventricular septum; PA-VSD, pulmonary atresia with ventricular septal defect; SD, standard deviation; TA, tricuspid atresia; TGA, transposition of the great arteries.

operation in 2, epicardial pacemaker insertion in 2, and other concomitant procedures in 11.

The majority of the LT Fontan procedures were performed across 5 major centers (295 patients), with a minority undergoing Fontan completion at smaller or international centers (6 patients).

Early Outcomes

There were 13 hospital mortalities (4%). Causes of death were low cardiac output in 5 patients, sepsis in 3, massive pulmonary emboli in 2, hemorrhagic stroke in 2, and unknown in 1 patient. No deaths occurred out of hospital within the first 30 days after surgery. A total of 4 patients underwent Fontan takedown during the initial hospital stay because of low cardiac output syndrome in 2 patients, prolonged chylous effusions with obstruction of the LT conduit in 1 patient, and thrombosis of the Fontan circuit in 1 patient.

The median length of hospital stay was 13 days (IQR: 9-19 days). Prolonged effusions occurred in 23 patients (8%), of whom 11 underwent reoperation (pleurodesis in 6, Fontan takedown or revision in 4, and fenestration dilatation in 1) and resulted in an increase in the median length of stay of 58 days (IQR: 38-79).

In 30 patients (10%), the length of stay exceeded 30 days and was attributable to prolonged pleural effusions in 16 patients, low cardiac output syndrome in 6 patients, persisting arrhythmias in 3 patients, stroke in 2 patients, pneumonia in 2 patients, and pericardial tamponade in 1 patient. There were no independent predictors for having prolonged pleural effusions.

Two patients required mechanical circulatory support (1 ECMO and 1 VAD) with the former subsequently undergoing an early Fontan takedown on postoperative day 2, and the latter dying on postoperative day 8 from persisting low cardiac output and renal failure. Early failure (death, takedown, revision, or ECMO and VAD) occurred in 21 patients (7%). On multivariable logistic regression, there were no independent predictors of early Fontan failure.

Clinical evidence of perioperative cerebral infarction was observed in 20 patients (7%) during the Fontan admission. These consisted of embolic stroke in 10 patients, hemorrhagic stroke in 3 patients, and cerebral ischemia secondary to a low output state in 7 patients.

Follow-up

After excluding patients who moved overseas and were followed up internationally (8 patients), hospital mortalities (13 patients), and those who had a Fontan takedown during the initial hospital stay (4 patients), 276 patients remained for survival analysis. Late follow-up was available in 275 patients (99.6%). Survival analysis was undertaken on 4749 patient-years of follow-up. The median duration of follow-up was 18.6 years (IQR: 15.1-21.1).

Survival

The overall survival at 10, 15, 20, and 25 years was 92% (95% confidence interval [CI]: 88%-95%), 90% (95% CI: 86%-93%), 86% (95% CI: 81%-90%), and 80% (95% CI: 69%-91%), respectively. Late survival of patients discharged alive with an intact Fontan circulation (N = 276) at 10, 15, 20, and 25 years was 97% (95% CI: 94%-99%), 95% (95% CI: 92%-98%), 91% (95% CI: 87%-95%), and 85% (95% CI: 74%-96%), respectively. The competing events' cumulative incidence curves for all patients are displayed in Figure 1. There were 21 late deaths. The causes of death were low cardiac output syndrome in 4 patients, stroke in 3 patients, intractable ventricular arrhythmias in 3 patients, massive pulmonary embolism in 2 patients, sepsis in 2 patients, pulmonary hemorrhage in 1 patient, protein-losing enteropathy in 1 patient, traumatic injury in 1 patient, and unknown in 4 patients. Independent predictors of late mortality are displayed in Table 2.

Late Failure and Reintervention

Late failure occurred in 45 hospital survivors discharged with an intact Fontan circulation, consisting of 21 late deaths, 4 heart transplantations, 7 conversions to ECC, 1 Fontan takedown, 9 cases of protein-losing enteropathy or plastic bronchitis, and 3 patients who where classified as NYHA Class III at last follow-up. Freedom from late failure was 91% (95% CI: 88%-95%) at 10 years, 88%

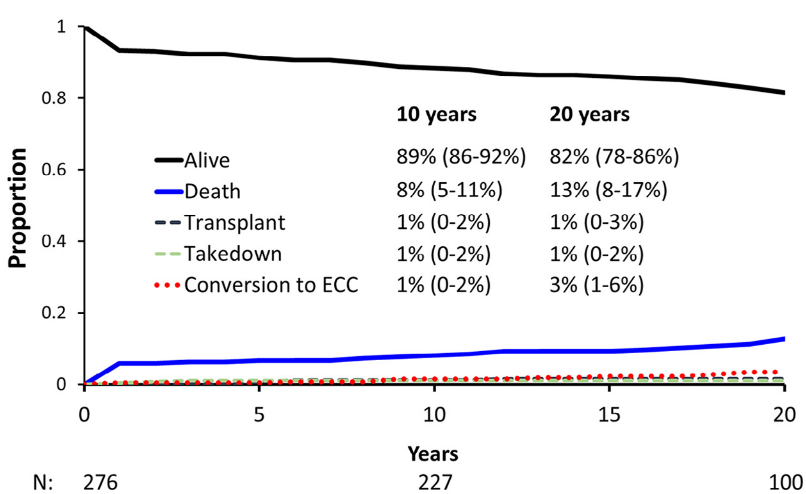

Figure 1. Competing events' cumulative incidence curves for all patients (N = 301). Late survival after the lateral tunnel Fontan is excellent with an overall survival of 82% at 20 years. (Color version of figure is available online.)

Table 2. Results of Multivariable Cox Regression for Late Outcomes

Variable	Hazard Ratio	95% CI Lower	95% CI Upper	*P* Value
Predictors of late mortality				
Male	2.84	1.06	7.60	0.04
Pre-Fontan common atrioventricular valve regurgitation ≥moderate	6.29	1.30	30.45	0.02
Prolonged pleural effusions	8.11	2.97	22.16	<0.001
Predictors of late Fontan failure				
Development of SVT*	4.68	2.07	10.58	<0.001
Age >7 (vs 3-5) at Fontan	9.69	2.46	38.21	0.001
Prolonged pleural effusions	3.06	1.05	8.95	0.04

*Development of SVT was analyzed as a time-dependent covariate.

(95% CI: 84%-92%) at 15 years, 83% (95% CI: 78%-88%) at 20 years, and 82% (95% CI: 76%-87%) at 25 years (Fig. 2). Independent predictors of late failure are displayed in Table 2. Multivariable predictors of late mortality and failure before backward elimination are included in Appendices 1 and 2.

Major late reinterventions undertaken in hospital survivors discharged with an intact Fontan circulation consisted of Damus-Kaye-Stansel procedure in 7 patients, Fontan circuit revision in 6, maze procedure in 6, atrioventricular valve repair or replacement in 5, pulmonary artery reconstruction in 5, pleurodesis in 4, ligation of the left superior vena cava in 2, thoracic duct ligation in 2, aortic root replacement (Bentall procedure) in 2, neoaortic valve replacement in 1, aortic valve repair in 1, aortic root reconstruction in 1, and diaphragm plication in 1. Transcatheter intervention was performed in 26 patients (9%), with radiofrequency arrhythmia ablation in 11, embolization of venovenous or aortopulmonary collaterals in 6, occlusion of the left superior vena cava in 3, pulmonary artery angioplasty ± stent in 3, fenestration dilatation in 2, and coronary artery stenting in 1. The fenestration was closed in 35 of the 148 patients (24%) who had a primary fenestration.

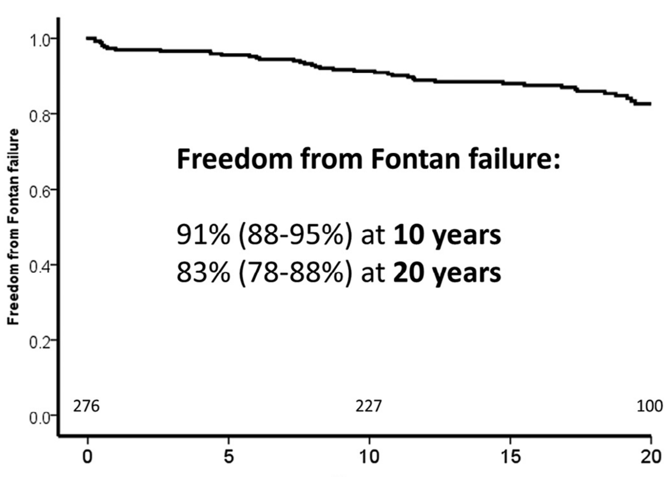

Figure 2. Freedom from Fontan failure for those surviving to hospital discharge with an intact Fontan circulation (N = 276). Late Fontan failure was defined as death, takedown, transplantation, Fontan conversion-revision, NYHA Class III or IV, protein-losing enteropathy, or plastic bronchitis.

Arrhythmia

A total of 38 patients (14%) developed SVT, and freedom from SVT at 10, 20, and 25 years was 90% (95% CI: 86%-93%), 76% (95% CI: 70%-82%), and 65% (95% CI: 55%-74%). Freedom from tachy- or bradyarrhythmias at 10 and 20 years was 87% (95% CI: 83%-91%) and 72% (95% CI: 66%-79%), respectively. On multivariable Cox regression analysis, only right atrial isomerism was independently associated with the development of SVT (HR 3.41, 95% CI: 1.35-8.64, $P = 0.009$).

Pacemakers were implanted in 41 patients (14%). Five patients had a pacemaker in situ at the time of Fontan, and the remaining 36 patients had a pacemaker inserted at the time of Fontan (2 patients), during the Fontan hospital stay (5 patients) or during follow-up (29 patients). Among the hospital survivors discharged with an intact Fontan circulation, freedom from pacemaker implantation at 10, 20, and 25 years were 89% (95% CI: 85%-93%), 84% (95% CI: 79%-89%), and 82% (95% CI: 76%-88%) respectively.

Anticoagulation and Thromboembolic Events

Of the 242 surviving patients with an intact LT Fontan at the last follow-up, 203 patients (84%) were on anticoagulation therapy or antiplatelet agents, consisting of warfarin in 108 patients (45%), aspirin in 89 patients (37%), low–molecular-weight heparins in 2 patients (0.8%), and a combination of agents in 4 patients (1.6%). No anticoagulation or antiplatelet agent was utilized in 29 patients (12%), and the method of anticoagulation was unknown in 10 patients (4%).

Symptomatic thromboembolism occurred in 45 patients (16%) during follow-up. These included 26 strokes, 9 pulmonary emboli, 7 transient ischemic attacks, 1 peripheral embolus, 1 renal embolus, and 1 paradoxical embolic myocardial infarction. Of the 45 patients who suffered a symptomatic thromboembolic event, 13 patients (29%) had a history of SVT. A further 22 patients had a thrombus detected within the conduit or central venous circulation on routine echocardiography during follow-up. Freedom from symptomatic thromboembolism at 10, 20, and 25 years was 93% (95% CI: 89%-96%), 80% (95% CI: 74%-86%), and 80% (95% CI: 74%-86%), respectively. On multivariable Cox regression analysis, pre-Fontan common atrioventricular valve regurgitation ≥ moderate (HR 9.34, 3.80-22.93, $P < 0.001$) and development of SVT (HR 2.67, 95% CI: 1.06-6.71, $P = 0.04$) were associated with thromboembolism. Age of <3 years at the time of Fontan was associated with a reduced likelihood of thromboembolism (HR 0.37, 95% CI: 0.15-0.88, $P = 0.02$). Ten of the 45 patients who experienced a symptomatic thromboembolic event during follow-up (22%) had a documented history of tachyarrhythmia before the event.

DISCUSSION

More than 25 years after its original description, the LT modification of the originally described Fontan procedure has demonstrated its superiority over the former AP Fontan. The 25-year survival of the patients discharged from the hospital with an intact LT circulation has reached a remarkable 85% within our population.

Estimates of late survival from the Mayo Clinic of 84%, 70%, and 39% at 10, 20, and 30 years after the LT Fontan, respectively, are less optimistic than our current series. The authors of this study have suggested that this may have been related to their large number of patients with heterotaxy syndromes and the incorporation of larger amounts of native atrial tissue into surgical repair, rendering their patients more susceptible to some of the complications observed after the AP connection.[10] Smaller patient numbers beyond 20 years in both instances are also likely to contribute to the observed discrepancies in survival estimates. Our series is a historical group of patients. One should be aware that, today, it is likely that the LT procedure would be reserved to very small patients because it avoids the need for implantation of a bulky adult-size conduit. In many centers, the LT procedure would therefore be reserved to patients with more severe conditions such as those with hypoplastic left heart syndrome (HLHS), which was present in only very small numbers in our series. It is therefore possible that contemporary results of the LT would be worse than those presented here.

Despite excellent survival rates, this population seems to be subjected to a slow but consistent failure of their Fontan circulation. We have now demonstrated that none of the 3 main types of Fontan circulation have experienced a sudden drop in their survival as was initially expected; however, there still seems to be constant rate of attrition over time.[11] The exact reasons for the failure of the Fontan circulation remain to be elucidated, and therefore the best way to prevent the decline is still unclear.[12-14] One may be surprised to notice a discrepancy between the large number of patients with a failed Fontan circulation and the small number of those requiring heart transplantation. This phenomenon has been observed worldwide and is attributed to the complexity of undertaking transplantation in these patients, the risk to undergo the procedure, and inequality of access to transplantation.[10,15,16] The LT technique was primarily introduced to decrease the rate of arrhythmias developing after Fontan completion, and it seems that it has achieved this goal.[5] We have previously demonstrated that the incidence of arrhythmias was significantly decreased by the introduction of the LT technique, which is again supported by our 20-year overall freedom from arrhythmias of around 70% of patients.[2]

Although ongoing failure and late onset of arrhythmia were not unexpected findings, we can now demonstrate that late failure is associated with the eventual occurrence of arrhythmias. The onset of arrhythmias has been shown to predict mortality in other Fontan populations around the world.[17] However, it must be acknowledged that the development of arrhythmias may indeed be just 1 manifestation of a failing Fontan.

We may face a similar phenomenon that was earlier observed in the patients with an AP connection, albeit at a later stage. In the LT Fontan, half of the venous circuit draining the blood from the inferior vena cava to the pulmonary arteries is made of native atrial tissue. With time, this atrial tissue may dilate and this stretch of the atrial wall, in conjunction with the long suture lines, may form triggers for supraventricular tachyarrhythmias. Atrial stretching may occur at a later stage than in patients with an AP connection as the wall stress is reduced by the elimination of turbulent flow within the atrium. Serial imaging of the LT conduit may be useful to aid risk stratification; however, this is yet to be fully investigated.

The incidence of thromboembolic events, as well as the number of massive pulmonary emboli, seems to be increased compared to what we have observed at the same time points in our ECC cohort. The reasons for this are unclear, although the increased turbulence within a dilated atrial channel may predispose to later thrombus formation.[18] This finding is supported by the additional number of patients in the current study who were noted to have a thrombus present within the LT Fontan circuit.

Limitations

The incidence of arrhythmias, particularly those that were intermittent or transient in nature, may be underestimated because of the limited availability of Holter monitoring or serial electrocardiography data.

Because of the low number of patients with HLHS in the present study, we were unable to draw any significant association between HLHS morphology and an increased risk of adverse events, failure, or mortality.

Another important limitation is the inability to accurately assess NYHA status retrospectively from medical records. The numbers derived for late Fontan failure may therefore not reflect the true burden of symptoms and noncardiac morbidities.

Prolonged pleural effusions were defined in the present study as lasting for more than 30 days, a definition that differs from that of other institutions that have used more than 14 days. This is definition is based on how the data have been collected in the Registry.

CONCLUSION

Over a 25-year period, the LT technique has achieved excellent late survival. As this population ages, it faces an increasing risk of failure and adverse events, including arrhythmia and thromboembolism. We are likely to see a growing number of these survivors requiring heart transplantation and late reintervention. Efforts must be made to develop treatment strategies for the increasing number of Fontan patients who will continue to experience attrition over time.

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APPENDIX 1. MULTIVARIABLE PREDICTORS OF LATE MORTALITY BEFORE BACKWARD ELIMINATION

	HR	95% CI for HR		*P* Value
		Lower	Upper	
Prolonged postoperative pleural effusions	8.982	2.026	39.822	.004
Development of SVT	4.973	1.449	17.063	.011
Pre-Fontan atrioventricular valve regurgitation ≥ moderate	9.834	1.438	67.267	.020
Prior PA banding	4.019	1.091	14.806	.037
Male	2.698	.844	8.617	.094
Prior aortic arch intervention	.288	.042	1.970	0.20
Age 5-7 (vs 3-5)	.543	.093	3.177	0.50
Prior BCPS	.613	.147	2.562	0.50
Fenestration at Fontan	.675	.212	2.151	0.51
LV dominance	1.240	.481	3.196	0.66
Age <3 (vs 3-5)	.742	.155	3.546	0.71
Age >7 (vs 3-5)	1.315	.292	5.912	0.72
Era 1990-1999 (vs pre-1990)	1.143	.248	5.275	0.86
Era 2000-2014 (vs pre-1990)	.000	n/a	n/a	0.99
HLHS	.000	n/a	n/a	0.99

BCPS, bidirectional cavopulmonary shunt; CI, confidence interval; HLHS, hypoplastic left heart syndrome; HR, hazard ratio; LV, left ventricle; n/a, not applicable; PA, pulmonary artery; SVT, supraventricular tachycardia.

APPENDIX 2. MULTIVARIABLE PREDICTORS OF LATE FAILURE BEFORE BACKWARD ELIMINATION

	HR	95% CI for HR		Sig.
		Lower	Upper	
Development of SVT	5.294	2.271	12.338	<0.0001
Prolonged effusions	3.510	1.131	10.890	.030
Age > 7 (vs 3-5)	2.648	.867	8.089	.087
Pre-Fontan atrioventricular valve regurgitation	2.507	.448	14.032	0.30
Fenestration	.629	.258	1.532	0.31
HLHS	3.524	.302	41.175	0.32
Age 5-7 (vs 3-5)	1.618	.494	5.300	0.43
Male	1.360	.633	2.922	0.43
Era 2000-2015 (vs pre-1990)	.379	.031	4.672	0.45
Era 1990-1999 (vs pre-1990)	.725	.267	1.968	0.53
LV dominance	1.228	.627	2.403	0.55
Prior BCPS	1.339	.512	3.500	0.55
Age <3 (vs 3-5)	1.152	.358	3.703	0.81
Prior aortic arch	.882	.221	3.525	0.86
Prior PA banding	.999	.360	2.771	1.00

BCPS, bidirectional cavopulmonary shunt; CI, confidence interval; HLHS, hypoplastic left heart syndrome; HR, hazard ratio; LV, left ventricle; PA, pulmonary artery; SVT, supraventricular tachycardia.

REFERENCES

1. Iyengar AJ, Winlaw DS, Galati JC, et al: The Australia and New Zealand Fontan Registry: Description and initial results from the first population-based Fontan registry. Intern Med J 44:148-155, 2014
2. d'Udekem Y, Iyengar AJ, Cochrane AD, et al: The Fontan procedure: Contemporary techniques have improved long-term outcomes. Circulation 116:I157-I164, 2007
3. Fontan F, Baudet E: Surgical repair of tricuspid atresia. Thorax 26:240-248, 1971
4. Lardo AC, Webber SA, Friehs I, et al: Fluid dynamic comparison of intra-atrial and extracardiac total cavopulmonary connections. J Thorac Cardiovasc Surg 117:697-704, 1999
5. de Leval MR, Kilner P, Gewillig M, et al: Total cavopulmonary connection: A logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg 96:682-695, 1988
6. Iyengar AJ, Winlaw DS, Galati JC, et al: The extracardiac conduit Fontan procedure in Australia and New Zealand: Hypoplastic left heart syndrome predicts worse early and late outcomes. Eur J Cardiothorac Surg 46:465-473, 2014
7. Stewart RD, Pasquali SK, Jacobs JP, et al: Contemporary Fontan operation: Association between early outcome and type of cavopulmonary connection. Ann Thorac Surg 93:1254-1260, 2012
8. d'Udekem Y, Iyengar AJ, Galati JC, et al: Redefining expectations of long-term survival after the Fontan procedure: Twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 130:S32-S38, 2014
9. Scrucca L, Santucci A, Aversa F: Competing risk analysis using R: An easy guide for clinicians. Bone Marrow Transplant 40:381-387, 2007
10. Pundi KN, Johnson JN, Dearani JA, et al: 40-Year follow-up after the Fontan operation: Long-term outcomes of 1,052 patients. J Am Coll Cardiol 66:1700-1710, 2015
11. Schilling C, Dalziel K, Nunn R, et al: The Fontan epidemic: Population projections from the Australia and New Zealand Fontan Registry. Int J Cardiol 219:14-19, 2016
12. de Leval MR, Deanfield JE: Four decades of Fontan palliation. Nat Rev Cardiol 7:520-527, 2010
13. Rychik J: The relentless effects of the Fontan paradox. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 19:37-43, 2016
14. Ohuchi H: Adult patients with Fontan circulation: What we know and how to manage adults with Fontan circulation? J Cardiol 2016, http://dx.doi.org/10.1016/j.jjcc.2016.04.001
15. Shi WY, Yong MS, McGiffin DC, et al: Heart transplantation in Fontan patients across Australia and New Zealand. Heart 102:1120-1126, 2016
16. Iyengar AJ, Sharma VJ, Weintraub RG, et al: Surgical strategies to facilitate heart transplantation in children after failed univentricular palliations: The role of advanced intraoperative surgical preparation. Eur J Cardiothorac Surg 46:480-485, 2014
17. Giannakoulas G, Dimopoulos K, Yuksel S, et al: Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalization. Int J Cardiol 157:221-226, 2012
18. Iyengar AJ, Winlaw DS, Grigg LE, et al: No difference between aspirin and warfarin after extracardiac Fontan in a propensity score analysis of 475 patients. Eur J Cardiothorac Surg 2016, http://dx.doi.org/10.1093/ejcts/ezw159