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Original Article

Long-term outcome after atrioventricular valve surgery following modified Fontan operation

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Abstract *Objective:* The objective of this study was to evaluate the early and late results of atrioventricular valve surgery after Fontan operation. *Background:* Atrioventricular valve regurgitation is a known perioperative risk factor for Fontan operation. There are limited data on the outcomes of late atrioventricular valve surgery following Fontan operation. *Methods:* Patients who underwent atrioventricular valve surgery following Fontan procedure were identified from the Mayo Clinic Fontan database. Medical records were reviewed for pre-operative, operative, and post-operative clinical and haemodynamic data. All patients not known to be deceased were sent health status questionnaires. *Results:* A total of 61 patients (28 females) underwent atrioventricular valve surgery following Fontan procedure. The median age at atrioventricular valve surgery was 14 years. The median duration between Fontan and atrioventricular valve surgery was 4.7 years. Median follow-up was 9 years. There were a total of 32 (52%) deaths with 8 (13%) within 30 days of surgery. The 5-, 10-, and 15-year survival rates were 67%, 57%, and 45%, respectively. On follow-up, 44 of 61 (72%) had arrhythmias, 21 of 29 (72%) were symptomatic, and 12 of 61 (20%) developed protein-losing enteropathy. On multivariate analysis, reduced ventricular function and development of protein-losing enteropathy were associated with decreased survival. *Conclusion:* Atrioventricular valve surgery after Fontan procedure is associated with substantial late morbidity and mortality. Atrioventricular valve surgery in this cohort of patients portends poor long-term outcome and is associated with a high incidence of protein-losing enteropathy. Reduced ventricular function and development of protein-losing enteropathy were associated with decreased survival.

Keywords: Atrioventricular valve surgery; Fontan operation; outcome

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Background

Ever since the first report of a total atriopulmonary shunt by Fontan and Baudet in 1971, modifications of the Fontan procedure have extended the indications for this operation to a wide range of congenital cardiac defects unsuitable for biventricular repair.[1] Operative mortality has significantly decreased despite application of the operation to patients with complex forms of single ventricle and to those with haemodynamic or other parameters previously considered to carry higher risk. There has been a significant improvement in early survival from 75% to 83% in the 1970s to over 90% in the current era.[2–6] Despite improvements in surgical techniques that reduce perioperative mortality, these patients are far from "cured". Following modified Fontan procedure, patients face a lifetime risk of atrioventricular valve insufficiency, ventricular dysfunction, arrhythmias, thromboembolic complications, protein-losing enteropathy, functional deterioration, and reduced life expectancy.[7–9] Atrioventricular valve regurgitation is a known perioperative risk factor for Fontan

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operation.[8,10] In the majority, atrioventricular valve regurgitation is dealt with prior to or at the time of Fontan operation. There are limited data on the outcomes of late atrioventricular valve surgery following Fontan operation.

The objective of this study was to evaluate the early and late results of atrioventricular valve surgery after Fontan operation and to assess the effects of variables traditionally known to correlate with poor outcome, as well as the current health status of survivors.

Methods

Patient population

A total of 61 patients underwent atrioventricular valve surgery following Fontan operations at the Mayo Clinic from 1972 to 2007. These patients were identified from the Mayo Clinic Fontan database. We obtained institutional review board approval for this study. No patients who had atrioventricular valve surgery following Fontan procedure were excluded. Hospital and outpatient records were abstracted for pre-operative, operative, and post-operative clinical and haemodynamic data. In addition, all patients who were not known to be deceased were sent health status questionnaires. Atrioventricular valve anatomy and systemic ventricular morphology were classified on the basis of findings from the pre-operative cardiac catheterisation and echocardiogram, as well as from operative findings. Discrepancies were settled by consensus of the authors. Current addresses and date of death were cross-referenced with Accurint, a locate-and-research database. Patients who did not return their questionnaires after the first mailing received two additional mailings and a reminder by telephone. Atrioventricular valve regurgitation was judged as absent (0), mild (1), moderate (2), or severe (3) from pre-operative angiograms or from echocardiograms when angiographic information was not available. The various modifications of the Fontan operation were classified into three groups depending on the type of atriopulmonary connection conduit (if an atriopulmonary or atrioventricular conduit had been used), direct atriopulmonary anastomosis, and total cavopulmonary anastomosis with an intracardiac lateral tunnel. In all cases, the operation involved separation of the systemic and pulmonary venous return by excluding the systemic venous return from the systemic ventricle. If a patient was no longer alive with a Fontan circulation, the reason for failure was elicited from the medical record, referring physician, post-mortem report, and/or death certificate.

The primary outcome variable in this study was transplant-free survival, in other words absence of death or cardiac transplantation. Death was classified as either early or late, with early failure occurring within 30 days of the atrioventricular valve surgery. Relationships between survival and perioperative variables were evaluated. We used the same independent variables of interest that were used in previous outcome studies of the Fontan operation from the Mayo Clinic.[8,11–14] Univariate assessment of the association of variables with mortality was performed using chi-square and Wilcoxon rank sum tests. Cumulative survival was estimated using the Kaplan–Meier method. Models were constructed with Cox proportional-hazard models using a stepwise elimination of the non-significant variables performed using a p-value cut point to retain variables <0.05. For all other comparisons, two-tail p-values of $\leqslant 0.05$ were taken as evidence of findings not attributable to chance.

Results

Patients

Of the 61 patients included in this study, 28 (46%) were females. The median age at atrioventricular valve surgery was 14 years with a range of 3–41 years. The median duration between Fontan and atrioventricular valve surgery was 4.7 years with a range of less than 1 year to 20.2 years. The median follow-up was 9 years with a range of 0–28 years.

Anatomy

Tricuspid atresia was the most common anatomic diagnosis and was seen in 23 patients (38%), followed by double inlet left ventricle in 14 (23%), unbalanced atrioventricular septal defect in four (7%), double outlet right ventricle in four (7%), and other causes in six (10%). Of the patients, 11 (18%) had heterotaxy syndrome. The type of Fontan connection and previous palliative surgeries are listed in Tables 1 and 2.

Atrioventricular valve and other surgeries

Left atrioventricular valve or mitral valve surgery was performed in 40 patients (66%) and right atrioventricular valve or tricuspid valve surgery in 14 patients (23%); a common atrioventricular valve morphology was seen in seven patients (11%). The atrioventricular valve was repaired in 38 patients (62%) and replaced in 23 (38%). In the repair cohort, post-operatively, the median atrioventricular valve regurgitation grade

Table 1. Type of Fontan connections.

Procedure	n (%)
Direct right atrium to pulmonary artery connection	28 (46)
Lateral tunnel Fontan	17 (28)
Intra-atrial conduit	16 (26)

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Table 2. Type of palliative surgical procedures before modified Fontan operation.

Procedure	n (%)
Blalock–Taussig shunt	28 (46)
Pulmonary artery band	5 (8)
Waterston shunt	17 (28)
Potts shunt	12 (20)
Kawashima	4 (6)

reduced from 3 to 1 ($p < 0.001$). In the repair group, five patients (four replacements and one re-repair; 13%) underwent atrioventricular valve reintervention on follow-up.

Fontan revision or takedown was performed in 19 patients (28%) at the time of atrioventricular valve surgery. Classic right atrium to pulmonary artery Fontan was converted to a lateral tunnel in four patients, and intra-atrial conduit was performed in five others. We performed one and a half ventricle repair in eight patients and the Fontan was taken down in two patients.

Mortality

Overall, 32 patients (52%) died during the follow-up period. Of them, eight patients (13%) died within 30 days of surgery (early death); cardiac failure was the most common cause of delayed mortality and was responsible for 12 deaths (20%); two patients (3%) died of sudden cardiac death; protein-losing enteropathy was responsible for four deaths (6.5%) and four patients (6.5%) underwent cardiac transplant. Clinical or autopsy data could not be obtained for two of the 32 patients. However, accurate dates of death were available for all the 32 patients.

Actuarial cumulative survival at 5, 10, and 15 years was 67%, 57%, and 45%, respectively (Figs 1 and 2).

Univariate and multivariate predictors of mortality

The variables that correlated significantly with mortality were ventricular dysfunction (subjectively assessed systolic function) before surgery ($p < 0.001$; hazard ratio = 5) and development of protein-losing enteropathy ($p < 0.0001$; hazard ratio = 6.1). The important factors not affecting survival included patient demographics, underlying anatomic diagnosis, heterotaxia syndromes, ventricular morphology, atrioventricular valve repair versus replacement, degree of atrioventricular valve regurgitation before surgery, bypass time, type of Fontan, concomitant surgeries, and era of surgery.

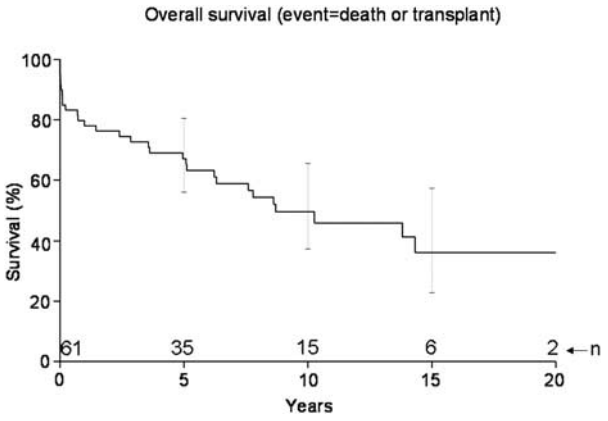

Figure 1.
Kaplan–Meier survival curve displays the overall transplant-free survival following atrioventricular valve surgery following Fontan procedure. (n = number at risk).

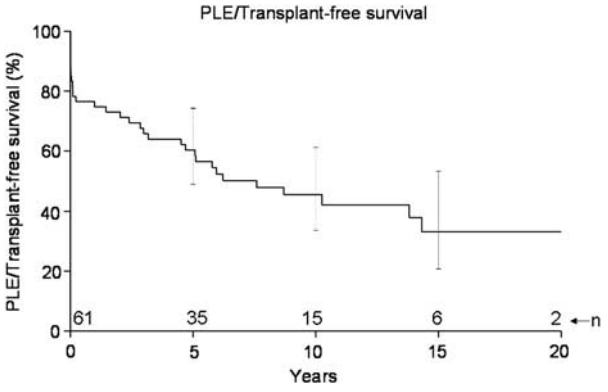

Figure 2.
Kaplan–Meier survival curve displays transplant- and protein-losing enteropathy (PLE)-free survival following atrioventricular valve surgery following Fontan procedure. (n = number at risk).

Current health and functional status

On follow-up, 44 patients (72%) developed arrhythmias, 17 (28%) required pacemaker placement, and 12 (20%) developed protein-losing enteropathy. All patients who developed protein-losing enteropathy did so within 7 years following atrioventricular valve surgery (Fig 2). Thromboembolic episodes occurred in nine patients (15%), including two with residual neurological deficits. Excluding the 32 total deaths, current health and functional status were available in 25 patients (86%). Of them, 16 (64%) reported having no or mild symptoms with ordinary physical activity; 14 (56%) were employed, and of these 50% worked full time and the remaining were part-time employees. All patients were on greater than 1 medications. The most common medications were angiotensin-converting enzyme inhibitor or angioten-

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sin II receptor blocker (85%), beta-blockers (45%), digoxin (35%), warfarin (30%), and diuretics (25%). There were four patients who had successful pregnancies following atrioventricular valve surgery.

Discussion

Ever since the initial description of selection criteria for Fontan operation by Choussat et al, advances in pre-operative risk evaluation, surgical technique and experience, and post-operative management have liberalised these criteria for Fontan patients.[15] However, atrioventricular valve regurgitation is considered a risk factor for operative mortality in patients with single ventricles undergoing modified Fontan procedure.[8,16–20] Moderate-to-severe atrioventricular regurgitation has been demonstrated in up to 20% of patients with single ventricle physiology.[5] In the majority of single ventricle patients with atrioventricular valve regurgitation, the valve is repaired or replaced at the time of Fontan procedure.[3] In some studies, the concomitant repair of the atrioventricular valve during Fontan procedure increased the mortality rate while other studies report no significant change.[3,21–23] In addition, studies have observed a progressive deterioration in the competency of the atrioventricular valve following the Fontan operation in patients without any prior atrioventricular valve operation.[10] However, there is a lack of systematic studies looking at the long-term outcome of this high-risk cohort. This study confirms our suspicion of the poor long-term outcome of patients undergoing late atrioventricular valve repair or replacement following Fontan procedure. Patients achieved a significant reduction in the degree of regurgitation following surgical repair. However, 10-year survival was only 57%. The incidence of protein-losing enteropathy is significantly high in this cohort. On follow-up, 20% of patients developed protein-losing enteropathy. All patients who developed protein-losing enteropathy did so within 7 years following atrioventricular valve surgery. Cardiac failure was the most common cause of delayed mortality. In survivors, late morbidity and mortality remain substantial.

Mechanistic origins of protein-losing enteropathy following the Fontan operation are not fully understood. However, two factors – low cardiac output and mesenteric inflammation – are thought to be primarily responsible for protein-losing enteropathy following Fontan.[24] Low cardiac output resulting from inefficient Fontan circulation leads to reduced mesenteric blood flow and elevated mesenteric vascular resistance resulting in protein-losing enteropathy.[24] Incidence of protein-losing enteropathy in this study cohort was significantly higher (20%). We speculate that, in this cohort, a combination of factors including atrioventricular valve regurgitation, reduced ventricular function, and elevated ventricular end-diastolic pressure lead to further reduction in cardiac output and higher incidence of protein-losing enteropathy. Atrioventricular valve regurgitation increases atrial pressure, resulting in decreased ventricular preload and diminished cardiac output. A myriad of treatment strategies including high-dose steroids, low molecular weight heparin, sildenafil, and catheter fenestration were tried with no significant or sustained improvement. On follow-up, four out of 12 patients died secondary to protein-losing enteropathy and two patients underwent cardiac transplantation. The incidence of protein-losing enteropathy in Fontan patients requiring AV valve surgery is high. The onset of protein-losing enteropathy heralds poor prognosis with limited treatment options.

In this study, two key factors modulated long-term mortality. These two factors include the presence of ventricular dysfunction and development of protein-losing enteropathy. Several previously recognised factors such as type of Fontan, ventricular morphology, underlying diagnosis, valve repair versus replacement, and era of surgery were not predictive of outcome.

Conclusion and limitations

We conclude that late onset atrioventricular valve regurgitation in patients with Fontan circulation is amenable to repair or replacement. However, late morbidity and mortality remain substantial in this group of patients. The incidence of protein-losing enteropathy is significantly higher than that for the rest of the Fontan group. Issues related to the atrioventricular valve may be best addressed prior to or at the time of Fontan operation. Patients needing atrioventricular valve surgery after Fontan have a long-term outcome that is inferior to other patients.

This was a retrospective review and the selection process was not randomised. The groups were not free from selection bias as the choice of intervention depended on the degree of atrioventricular valve regurgitation as well as the surgeons' preference. The repair techniques were also not standardised. Patients with very severe degrees of atrioventricular valve regurgitation and ventricular dysfunction may not have been referred for surgery and therefore this study group could not be representative of every patient with this problem.

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References

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240–258.
2. Khairy P, Fernandes SM, Mayer Jr JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008; 117: 85–92.
3. Kerendi F, Kramer ZB, Mahle WT, et al. Perioperative risks and outcomes of atrioventricular valve surgery in conjunction with Fontan procedure. Ann Thorac Surg 2009; 87: 1488–1489.
4. Hirsch JC, Goldberg C, Bove EL, et al. Fontan operation in the current era: a 15-year single institution experience. Ann Surg 2008; 248: 402–410.
5. Anderson PA, Sleeper LA, Mahony L, et al. Pediatric heart network investigators. Contemporary outcomes after the Fontan procedure: a pediatric heart network multicenter study. J Am Coll Cardiol 2008; 52: 85–98.
6. Hosein RB, Clarke AJ, McGuirk SP, et al. Factors influencing early and late outcome following the Fontan procedure in the current era. The 'Two Commandments'? Eur J Cardiothorac Surg 2007; 31: 344–352.
7. Khairy P, Poirier NC, Mercier LA. Univentricular heart. Circulation 2007; 115: 800–912.
8. Driscoll DJ, Oxfford KP, Feldt RH, et al. 5–15 year follow-up after Fontan operation. Circulation 1992; 85: 469–496.
9. Bartz PJ, Driscoll DJ, Dearani JA, et al. Early and late results of the modified fontan operation for heterotaxy syndrome 30 years of experience in 142 patients. J Am Coll Cardiol 2006; 48: 2301–2305.
10. Gentles TL, Mayer JE Jr, Gauvreau K, et al. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. J Thorac Cardiovasc Surg 1997; 114: 376–391.
11. Humes RA, Feldt RH, Porter CJ, et al. The modified Fontan operation for asplenia and polysplenia syndromes. J Thorac Cardiovasc Surg 1988; 96: 212–218.
12. Earing MG, Cetta F, Driscoll DJ, et al. Long-term results of the Fontan operation for double-inlet left ventricle. Am J Cardiol 2005; 96: 291–298.
13. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25-year experience with 216 patients. J Am Coll Cardiol 2001; 37: 933–939.
14. Cetta F, Feldt RH, O'Leary PW, et al. Improved early morbidity and mortality after Fontan operation: the Mayo clinic experience, 1987 to 1992. J Am Coll Cardiol 1996; 28: 480–486.
15. Choussat A, Fontan F, Besse P, et al. Selection criteria for Fontan procedure. In: Anderson RH, Shinebourne EA, editor. Pediatric Cardiology. Churchill Livingstone, Edinburg, 1978, 559–566.
16. d'Udekem Y, Iyengar AJ, Cochrane AD, et al. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 2007; 116: I157–164.
17. Gersony WM. Fontan operation after 3 decades: what we have learned. Circulation 2008; 117: 13–15.
18. Knott-Craig CJ, Danielson GK, Schaff HV, et al. The modified Fontan operation. An analysis of risk factors for early post-operative death or takedown in 702 consecutive patients from one institution. J Thorac Cardiovasc Surg 1995; 109: 1237–1243.
19. Lamberti JJ, Mainwaring RD, Spicer RL, et al. Factors influencing perioperative morbidity during palliation of the univentricular heart. Ann Thorac Surg 1995; 60: S550–S553.
20. Imai Y, Takanashi Y, Hoshino S, et al. Modified Fontan procedure in ninety-nine cases of atrioventricular valve regurgitation. J Thorac Cardiovasc Surg 1997; 113: 262–268.
21. Uemura HYT, Kawashima Y, Yamamoto F, et al. What factors affect ventricular performance after a Fontan-type operation? J Thorac Cardiovasc Surg 1995; 110: 405–415.
22. Reyes A 2nd, Bove EL, Mosca RS, et al. Tricuspid valve repair in children with hypoplastic left heart syndrome during staged surgical reconstruction. Circulation 1997; 96: II344–II345.
23. Sallehuddin A, Bulbul Z, Otero F, et al. Repair of atrioventricular valve regurgitation in the modified Fontan operation. Eur J Cardiothorac Surg 2004; 26: 54–59.
24. Rychik J. Forty years of the Fontan operation: a failed strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010; 13: 96–100.

Appendix

List of factors assessed that were "non-significant" in the univariate model

1. Age at surgery
2. Gender
3. Era of surgery
4. Primary cardiac lesion
5. Heterotaxy syndrome
6. Number of previous palliations
7. Ventricular morphology
8. Valve morphology
9. Type of Fontan connection
10. Age at Fontan
11. Duration between Fontan and atrioventricular valve surgery
12. Bypass time and cross-clamp time (minutes)
13. Post-operative duration of hospitalisation
14. Post-operative renal failure
15. Concomitant surgeries
16. Arrhythmias
17. Use of antiarrhythmic or diuretic medications
18. Pacemaker

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