Long-term outcomes of single-ventricle palliation for unbalanced atrioventricular septal defects: Fontan survivors do better than previously thought

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ABSTRACT

Background: Single-ventricle palliation (SVP) for children with unbalanced atrioventricular septal defect (uAVSD) is thought to carry a poor prognosis, but limited data have been reported.

Methods: We performed a retrospective review of children with uAVSD who underwent SVP at a single institution. Data were obtained from medical records and correspondence with general practitioners and cardiologists.

Results: Between 1976 and 2016, a total of 139 patients underwent SVP for uAVSD. A neonatal palliative procedure was performed in 83.5% of these patients (116 of 139), and early mortality occurred in 11.2% (13 of 116). Ninety-four patients underwent stage II palliation, with an early mortality of 6.4% (6 of 94). Eighty patients (57.6%) underwent Fontan completion, with an early mortality of 3.8% (3 of 80). Interstage mortality was 11.7% (12 of 103) between stages I and II and 17.0% (15 of 88) between stage II and Fontan.

Long-term survival was 66.5% (95% confidence interval [CI], 57.9%-73.9%) at 5 years, 64.4% (95% CI, 55.5%-72.0%) at 15 years, and 57.8% (95% CI, 47.5%-66.8%) at 25 years. Survival post-Fontan was 94.9% (95% CI, 86.9%-98.0%) at 5 years, 92.0% (95% CI, 80.6%-96.8%) at 15 years, and 82.4% (95% CI, 61.5%-92.6%) at 25 years. Risk factors associated with death or transplantation were aortic atresia (hazard ratio [HR], 5.3; $P = .03$) and hypoplastic aortic arch (HR, 2.5; $P = .02$). Atrioventricular valve operations were required in 31.7% of the patients (44 of 139), with 31.8% of them (14 of 44) requiring a further operation.

Conclusions: Children undergoing SVP for uAVSD have substantial mortality, with <60% survival at 25 years. However, survival of children who achieve Fontan completion is better than has been reported previously. (J Thorac Cardiovasc Surg 2017;153:430-8)

Freedom from death or transplantation for patients with uAVSD undergoing single ventricle palliation.

Central Message

Patients with unbalanced atrioventricular septal defects who achieve Fontan completion have better survival than was previously thought.

Perspective

Single ventricle palliation for unbalanced atrioventricular septal defects is associated with substantial mortality, with <60% survival at 25 years. However, in those who achieve Fontan completion, survival is similar to that of the general Fontan population. Management of the atrioventricular valve (AVV) remains a challenge, with almost one-third of patients requiring AVV surgery.

See Editorial Commentary page 439.

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Children with unbalanced atrioventricular septal defect (uAVSD) constitute approximately 10% of all patients with atrioventricular septal defect (AVSD).^{1,2} The majority of these children undergo single-ventricle palliation (SVP). Children undergoing SVP for uAVSD have been shown to have a particularly poor prognosis.²⁻⁵

Scanning this QR code will take you to the article title page.

Abbreviations and Acronyms

AVSD	= atrioventricular septal defect
AVV	= atrioventricular valve
AVVR	= atrioventricular valve regurgitation
BCPS	= bidirectional cavopulmonary shunt
HLHS	= hypoplastic left heart syndrome
LV	= left ventricle
PA	= pulmonary artery
PDA	= patent ductus arteriosus
SVP	= single-ventricle palliation
TAPVD	= total anomalous pulmonary venous drainage
uAVSD	= unbalanced atrioventricular septal defect

In series published to date, only one-third of patients with uAVSD achieved Fontan completion, and nearly 40% of those who achieved Fontan completion died by 2.5 years of follow-up.^{2,3} Furthermore, reports on the long-term follow-up of this challenging group of patients are limited.³ We retrospectively reviewed our experience of SVP in children with uAVSD.

METHODS

Patients

All patients with uAVSD who underwent SVP at the Royal Children's Hospital, Melbourne between January 1, 1976, and January 1, 2016, were included in the study. Ethics approval was granted by the Royal Children's Hospital's Human Research Ethics Committee (HREC 32047E). International patients were excluded, because follow-up data were not available for this group.

Here uAVSD was defined as a complete AVSD, as confirmed on echocardiography, which in the opinion of the treating team was not suitable for biventricular repair (ie, the ventricles could not be septated), owing to either a hypoplastic ventricle or a straddling atrioventricular valve (AVV). Baseline data were collected by retrospective chart review. Follow-up data were obtained by correspondence with the patients' general practitioners and cardiologists. Follow-up was considered complete if the last confirmed patient contact occurred within 2 years of the end of the study period. Early death was defined as death occurring within 30 days after surgery or before discharge from the hospital. Significant AVV regurgitation was defined as moderate or greater AVV regurgitation as assessed on echocardiography.

Stage I palliation was defined as either the Norwood procedure or other procedures. These other procedures included pulmonary artery band, Damus–Kaye–Stansel connection, repair of total anomalous pulmonary venous drainage (TAPVD), ligation of a patent ductus arteriosus (PDA), pulmonary valvuloplasty, or right ventricle-to-pulmonary artery conduit. All Norwood procedures were performed after the year 2000. Stage II procedures were bidirectional cavopulmonary shunt (BCPS) operations. Stage III was Fontan completion.

Statistical Methods

All data were analyzed using Stata version 13 (StataCorp, College Station, Tex). All continuous data are expressed as mean $\pm$ standard deviation unless specified otherwise. Continuous data were compared between groups using the Mann–Whitney *U* test. Discrete variables were compared between groups using the χ^2 test, unless group size was <10 ,

in which case the Fisher exact test was used. Time-dependent endpoints, specifically survival and freedom from death and transplantation, were analyzed using the Kaplan–Meier method, with time commencing at the initial palliation for analysis of the overall cohort and at the individual stages for analyses of each stage of palliation. Risk factors evaluated in a univariable Cox regression were age, moderate or greater atrioventricular valve regurgitation (AVVR), heterotaxy syndrome, double-outlet right ventricle, year of operation (in days since 1976, scaled to years), aortic atresia, aortic arch hypoplasia, hypoplastic pulmonary arteries (PAs), chromosomal abnormality, hypoplastic left ventricle (LV), and Norwood procedure as stage I palliation.

Variables with at least moderate evidence against the null hypothesis ($P < .10$) were included in a multivariable model. Specifically, for stage I and stage II procedures, a competing risks model was used for survival analysis, where follow-up time was defined as the interval between the relevant stage and last follow-up, death, transplantation, or progression to the next stage. Furthermore, for stage I and II, a competing risks regression was performed with a Fine and Gray proportional subhazards model, using the same univariable predictors and threshold for inclusion in a multivariable model as in the Cox model described above. The threshold for statistical significance was $P < .05$.

RESULTS

A total of 139 patients underwent SVP for uAVSD at the study institution between January 1, 1976, and January 1, 2016. Follow-up was complete for all patients. The mean follow-up time was 12.2 ± 14.4 years (median, 8.4 years; interquartile range [IQR], 1.1–21.1 years). The baseline demographic data are summarized in [Table 1](#). The procedures are summarized in [Figure 1](#).

Stage I Procedures

Of the 139 children, 16.5% (23 of 139) did not undergo a stage I procedure, including 12.2% (17 of 139) who proceeded directly to stage II and 4.3% (6 of 139) who proceeded directly to Fontan. The remaining 83.5% of patients (116 of 139) underwent a stage I procedure ([Table 2](#)). The median age at the time of stage I palliation was 11.5 days (IQR, 4.0–63.9 days; mean, 112.8 ± 378.0 days). The mean age at stage I was 233.6 ± 545.7 days in those operated on before the year 2000, but decreased to 18.3 ± 31.8 days in those operated on from 2000 onward ($P = .002$). At least one additional concomitant cardiovascular procedure was performed in 50.0% of the patients (58 of 116). The most common concomitant procedures were PDA ligation (23.3%; 27 of 116), PA reconstruction (8.6%; 10 of 116), aortic arch repair (7.8%; 9 of 116), and TAPVD repair (6.9%; 8 of 116). Early mortality was 11.2% (13 of 116). The Norwood procedure was associated with a significantly greater risk of early mortality compared with other stage I procedures (45.5% vs 7.5%; $P = .003$). Early mortality was more frequent in patients who underwent additional concomitant procedures compared with those who did not, but the difference was not statistically significant (17.2% vs 5.2%; $P = .07$). Hypoplastic LV ($P = 1.0$), age at time of

TABLE 1. Demographic data

Variable	Value
Total number of patients	139
Sex, n (%)	
Male	79 (56.8)
Female	60 (43.2)
Ventricular dominance, n (%)	
Left	30 (21.6)
Right	94 (67.6)
Balanced	15 (10.8)
Additional cardiac anomalies, n (%)*	
Heterotaxy	102 (73.4)
DORV	72 (51.8)
Additional VSD (not inlet)	69 (49.6)
Bilateral SVC	59 (42.4)
Right atrial isomerism	48 (34.5)
Right aortic arch	45 (32.4)
Secundum ASD	45 (32.4)
Pulmonary atresia	43 (30.9)
Interrupted IVC	41 (30.2)
Left atrial isomerism	38 (27.3)
TGA	38 (27.3)
TAPVD	37 (26.6)
Dextrocardia	29 (20.9)
Aortic arch hypoplasia	21 (15.1)
Pulmonary artery hypoplasia	17 (12.2)
Aortic coarctation	16 (11.5)
MAPCAs	8 (5.8)
Aortic atresia	4 (2.9)
Moderate or greater AVVR at stage I, n (%)	20 (14.4)
Gastrointestinal malrotation, n (%)	31 (23.0)
Chromosomal abnormality, n (%)	11 (7.9)
Trisomy 21	4 (2.9)
Other	7 (5.0)

DORV, Double-outlet right ventricle; VSD, ventricular septal defect; SVC, superior vena cava; ASD, atrial septal defect; IVC, inferior vena cava; TGA, transposition of the great arteries; TAPVD, total anomalous pulmonary venous drainage; MAPCAs, major aortopulmonary collateral arteries; AVVR, atrioventricular valve regurgitation.

*All conditions with more than 2% of the cohort affected.

operation ($P = .11$) and surgery before 2000 ($P = .38$) were not predictive of early mortality.

Another 11.7% of patients (12 of 103) who survived stage I died before stage II palliation. Age at the time of stage I ($P = .45$), presence of hypoplastic LV ($P = 1.0$), additional procedures at the time of stage I ($P = .54$), and initial surgery before 2000 ($P = 1.0$) were not significantly predictive of the risk of interstage death.

Stage II Procedures

A stage II procedure was performed in 94 patients (Table 2). The median patient age at the time of stage II was 10.3 months (IQR, 4.4-20.3 months; mean, 19.2 ± 32.3 months), and the median interval between stage I and stage II procedures was 10.7 months (IQR, 3.96-20.4 months; mean, 16.7 ± 22.7 months). The mean

age at the time of stage II decreased significantly after 2000 (9.5 ± 9.4 months vs 33.6 ± 46.1 months; $P < .001$). An additional concomitant procedure was performed in 71.3% of the patients (67 of 94). The most frequently performed concomitant procedures were AVV repair (13.8%; 13 of 94), TAPVD repair (12.8%; 12 of 94), main PA division (12.8%; 12 of 94), and PA patch enlargement (9.6%; 9 of 94). Early mortality was 6.4% (6 of 94). Moderate or greater AVVR at the time of stage II was associated with increased early mortality (15.4% vs 2.9%; $P = .048$). Hypoplastic LV ($P = 1.0$), age at the time of stage II ($P = .13$), additional concomitant procedures ($P = .18$), and having undergone initial surgery before 2000 ($P = .68$) were not associated with increased risk of early mortality.

Among the patients who survived stage II palliation, another 17.0% (15 of 88) died without progressing to Fontan. Interstage mortality was less frequent after 2000, but this did not reach statistical significance (11.3% vs 25.7%; $P = .09$). Age at the time of stage II ($P = .37$), hypoplastic LV ($P = .55$), and additional procedures at the time of stage II ($P = 1.0$) did not predict an increased risk of interstage mortality.

Fontan Procedure

Eighty patients underwent Fontan completion, the details of which are summarized in Table 2. The median age at the time of Fontan completion was 5.8 years (IQR, 4.3-7.9 years; mean, 7.1 ± 5.5 years). The mean age at the time of Fontan has decreased in recent years, from 8.7 ± 6.9 years in those who underwent initial surgery before 2000 to 5.2 ± 2.1 years in those who underwent initial surgery from 2000 onward ($P = .004$). Additional procedures were performed in 40.0% of the patients (32 of 80), most frequently AVV surgery (15.0%; 12 of 80) and main pulmonary artery division (7.5%; 6 of 80). The median interval between the stage II procedure and Fontan completion was 4.3 years (IQR, 3.5-5.4 years; mean, 4.3 ± 3.5 years). Early mortality was 3.8% (3 of 80). Age at the time of Fontan ($P = .41$), hypoplastic LV ($P = .21$), significant AVVR before Fontan ($P = .45$), concomitant procedure ($P = .56$), type of Fontan ($P = 1.0$), and have undergone initial surgery before 2000 ($P = 1.0$) were not predictive of early mortality after Fontan completion.

Survival for the Whole Cohort

For the overall cohort, survival was 66.5 % (95% CI, 57.9%-73.9%) at 5 years, 64.4% (95% CI, 55.5%-72.0%) at 15 years, and 57.8% (95% CI, 47.5%-66.8%) at 25 years. There were 5 orthotopic cardiac transplantations (5 of 139; 3.6%). Freedom from death and transplantation was 66.5% (95% CI, 57.8%-73.8%) at 5 years, 61.8% (95% CI, 52.5%-69.8%) at 15 years, and

FIGURE 1. Procedures and outcomes.

55.2% (95% CI, 50.5%-64.5%) at 25 years (Figure 2, A). Univariable predictors of death or transplantation are summarized in Table 3. Aortic atresia (HR, 8.5; $P < .001$), hypoplastic aortic arch (HR, 3.2; $P < .001$), Norwood procedure (HR, 2.9; $P = .01$), and more recent initial surgery (HR, 1.03; $P = .04$) were associated with adverse outcomes. The factors entered into a multivariable model are listed in Table 4. Aortic atresia (HR, 5.3; $P = .03$)

and hypoplastic aortic arch (HR, 2.5; $P = .02$) were independently associated with increased risk of death or transplantation.

Survival Following Stage I

The competing risk model of outcomes following stage I palliation is shown in Figure 2, B. Univariable predictors of death or transplantation are listed in Table 3. In univariable analysis, aortic arch hypoplasia (HR, 3.1; $P = .01$) and Norwood procedure (HR, 3.2; $P = .03$) were predictive of death or transplantation, whereas hypoplastic PAs (HR, 0.11; $P = .03$) was predictive of decreased risk. In a multivariable model, significant AVVR at the time of stage I was predictive of decreased transplantation-free survival (HR, 2.5; $P = .03$) (Table 4).

Survival Following Stage II

The competing risk model of outcomes following stage II palliation is shown in Figure 2, C. Univariable predictors of death or transplantation are listed in Table 3. Aortic atresia was associated with increased risk of death or transplantation (HR, 10.6; $P < .001$). Because no other factors approached statistical significance, multivariable analysis was not performed.

Survival Following Fontan Operation

The mean follow-up time after Fontan completion was 12.3 ± 9.7 years (median, 9.3 years; IQR, 4.2-21.8 years). In the patients who underwent Fontan completion, survival was 94.9% (95% CI, 86.9%-98.0%) at 5 years, 92.0% (95% CI, 80.6%-96.8%) at 15 years, and 82.4% (95% CI, 61.5%-92.6%) at 25 years. Freedom from death, Fontan takedown, and transplantation was 89.7% (95% CI, 80.4%-94.7%) at 5 years, 83.5% (95% CI, 69.7%-91.3%) at 15 years, and 77.3% (95% CI,

TABLE 2. Type of procedure and early mortality by stage of palliation

Procedure	Number of procedures	Early mortality, n (%)
Stage I		
MBT	51	1 (2.0)
Isolated PAB	28	3 (10.7)
Central shunt	13	1 (7.7)
Norwood	11	5 (45.5)
DKS	7	2 (28.6)
PDA ligation	2	0 (0)
Isolated TAPVD repair	1	0 (0)
RV-PA shunt	1	1 (100)
Pulmonary valvuloplasty	2	0 (0)
Total	116	13 (11.2)
Stage II		
BCPS	41	4 (9.8)
Bilateral BCPS	31	2 (6.5)
Kawashima	22	0 (0.0)
Total	94	6 (6.4)
Stage III (Fontan)		
Extracardiac conduit	49	2 (4.1)
Lateral tunnel	21	1 (4.8)
atriapulmonary connection	10	0 (0.0)
Total	80	3 (3.8)

In cases where more than 1 operation was performed concomitantly, the dominant procedure is listed. MBT, Modified Blalock–Taussig shunt; PAB, pulmonary artery band; DKS, Damus–Kaye–Stansel connection; PDA, patent ductus arteriosus; TAPVD, total anomalous pulmonary venous drainage; RV-PA, right ventricle to pulmonary artery shunt; BCPS, bidirectional cavopulmonary shunt.

FIGURE 2. Kaplan–Meier freedom from death and transplantation for the entire cohort (A), competing risk model for stage I (B), competing risk model for stage II (C), and freedom from death, transplantation, and Fontan takedown in patients who underwent Fontan (time in years after Fontan completion) (D). *CI*, Confidence interval; *BCPS*, bidirectional cavopulmonary shunt.

57.6%–88.6%) at 25 years (Figure 2, D). In univariable analysis, only older age at the time of Fontan approached statistical significance as a predictor of death or transplantation (HR, 1.1; $P = .06$). Although chromosomal abnormalities were not predictive of adverse outcome, only 1 of 4 patients (25%) with trisomy 21 survived to Fontan.

At the end of the study period, 85.0% of the patients (68 of 80) were alive with a Fontan circulation. Late death occurred in 6.3% of these patients (5 of 80). Fontan takedown was performed in 5.0% of the patients (4 of 80), 1 of whom (1.3%) was still alive at last follow-up. Orthotopic cardiac transplantation was performed in 4 patients following the Fontan procedure (4 of 80; 5.0%), 2 of whom (2.5%) were alive at last follow-up. New York Heart Association (NYHA) functional class could be determined for 97.1% of the Fontan survivors (66 of 68) at their most recent follow-up; 83.3% (55 of 66) were in NYHA class I, 12.1% (8

of 66) were in NYHA class II, and 4.5% (3 of 66) were in NYHA class III. Late complications at the last follow-up included dysrhythmia in 35.0% (28 of 80), hepatic dysfunction in 13.8% (11 of 80), protein-losing enteropathy in 5.0% (4 of 80), and plastic bronchitis in 2.5% (2 of 80).

AVV Procedures

Additional procedures on the AVV were performed in 31.7% of the patients (44 of 139) because of AVVR. Of the initial procedures, 6.8% (3 of 44) were replacements, and the remaining 93.2% (41 of 44) were repairs. The timing of the initial AVV procedure based on the stage of palliation is shown in Table 5. Early mortality for initial AVV operations was 18.2% (8 of 44). Of those who underwent an AVV operation, 31.8% (14 of 44) required a second AVV operation, of which 64.3% (9 of 14) were repairs and 35.7% (5 of 14) were replacements. Another

TABLE 3. Univariable predictors of death or transplantation for the whole cohort, and each stage of palliation (Fontan take-down is included as failure in the Fontan group)

Variable	Whole cohort		Stage I		Stage II		Fontan	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.0 (0.95-1.1)	.80	0.1 (0.00-3.6)	.20	0.94 (0.74-1.2)	.62	1.1 (1.0-1.1)	.06
Aortic atresia†	8.5 (3.0-24.4)	<.001	3.5 (1.3-17.5)	.13	10.6 (4.3-26.3)	<.001	*	*
Arch hypoplasia	3.2 (1.7-6.0)	<.001	3.1 (1.4-7.1)	.01	1.8 (0.59-5.2)	.32	*	*
Chromosomal abnormality	0.88 (0.32-2.4)	.81	0.91 (0.21-3.9)	.90	2.4 (0.56-10.6)	.24	*	*
DORV	0.82 (0.49-1.4)	.64	0.56 (0.25-1.3)	.16	1.1 (0.47-2.6)	.84	1.6 (0.48-5.3)	.46
Heterotaxy	0.84 (0.48-1.5)	.55	0.78 (0.34-1.8)	.57	0.93 (0.33-2.6)	.89	0.81 (0.24-2.7)	.73
Hypoplastic LV	0.92 (0.53-1.6)	.78	1.1 (0.47-2.5)	.84	0.73 (0.31-1.7)	.48	0.95 (0.28-3.2)	.94
Hypoplastic PAs	0.62 (0.31-1.2)	.17	0.11 (0.01-0.84)	.03	1.1 (0.44-2.8)	.83	0.85 (0.23-3.8)	.85
Moderate or greater AVVR	1.8 (0.92-3.5)	.09	2.5 (0.99-6.3)	.05	1.7 (0.72-4.2)	.22	0.57 (0.07-4.5)	.59
Norwood procedure	2.9 (1.3-6.5)	.01	3.2 (1.1-9.3)	.03	1.4 (0.32-6.4)	.65	*	*
Year of procedure	1.03 (1.0-1.06)	.04	1.02 (0.99-1.1)	.15	0.97 (0.92-1.02)	.29	0.99 (0.92-1.1)	.71

Bold indicates the variable reaches statistical significance. HR, Hazard ratio; CI, confidence interval; DORV, double-outlet right ventricle; LV, left ventricle; PA, pulmonary artery; AVVR, atrioventricular valve regurgitation. *An insufficient number of patients survived to Fontan completion, precluding analysis. †Only 4 patients in total.

9.1% of patients (4 of 44) required a third AVV operation, which included 1 valve closure and 3 re-replacements. No patient required a fourth AVV operation.

Overall freedom from intervention on the AVV was 72.7% (95% CI, 62.7%-80.4%) at 5 years, 63.4% (95% CI, 52.8%-72.7%) at 15 years, and 63.4% (95% CI, 52.8%-72.7%) at 25 years. The risk of undergoing an intervention on the AVV was significantly lower in patients who underwent Fontan completion compared with those who did not (HR, 0.28; $P < .001$) (Figure 3, A). From the time of Fontan completion, freedom from AVV operation was 95.5% (95% CI, 86.7%-98.5%) at 5 years, and remained stable at 92.7% (95% CI, 80.8%-97.4%) at 15 and 25 years (Figure 3, B).

DISCUSSION

Unbalanced AVSD occurs in approximately 10% of patients with AVSD.^{1,2} A biventricular repair in children with uAVSD might not be feasible owing to either

hypoplasia of 1 ventricle, with or without override of the AVV, or straddling of the subvalvular apparatus, with 2 well-developed ventricles. The outcomes of SVP in children with uAVSD are rarely reported and generally have been poor.²⁻⁵ Early attempts at Fontan completion in the setting of uAVSD had poor results.^{4,5} More recently, only small series of patients with uAVSD undergoing SVP have been reported.^{2,3}

Drinkwater and colleagues² reported 45 patients with uAVSD who underwent SVP between 1986 and 1996. Only 16 of 45 patients (35.6%) progressed to Fontan completion. Of the patients who underwent the Fontan operation, 37.5% (6 of 16) had died at a mean follow-up of 2.5 years. More recently, Owens and colleagues³ reported 44 patients with uAVSD who presented between 1998 and 2003, 79.5% of whom (35 of 44) underwent SVP. Survival was 51% at a mean follow-up of 25 months. Only 16 of 44 patients (36.4%) progressed to Fontan completion. The authors did not report the long-term outcomes of patients who survived to Fontan.

In recent large reports of SVP outcomes, the subgroup with uAVSD constituted only a small proportion of the

TABLE 4. Multivariable predictors of death or transplantation

Multivariable predictor	HR (95% CI)	P value
Overall		
Aortic atresia	5.3 (1.2-23.0)	.03
Aortic arch hypoplasia	2.5 (1.1-5.5)	.02
≥Moderate AVVR	1.8 (0.84-4.0)	.13
Year of procedure	1.0 (0.98-1.0)	.39
Norwood procedure	0.82 (0.24-2.8)	.80
Stage I		
≥Moderate AVVR	2.5 (1.1-5.9)	.03
Hypoplastic PAs	0.17 (0.02-1.3)	.09
Aortic arch hypoplasia	2.1 (0.84-5.4)	.11
Norwood procedure	1.8 (0.6-5.5)	.32

HR, Hazard ratio; CI, confidence interval; AVVR, atrioventricular valve regurgitation; PA, pulmonary artery.

TABLE 5. Timing of AVV operations in relation to stage of SVP

Stage of SVP	n (%)
Total	44
Before stage I	1 (2.3)
At the time of stage I	1 (2.3)
Between stages I and II	4 (9.1)
At the time of stage II	17 (38.6)
Between stage II and Fontan	9 (20.4)
At the time of Fontan	10 (22.7)
After Fontan	2 (4.5)

SVP, Single-ventricle palliation.

FIGURE 3. Freedom from AVV operation in patients who underwent Fontan and those who did not (A) and freedom from AVV operation after Fontan completion (B). CI, Confidence interval; AVV, atrioventricular valve.

cohorts. A previous report from our institution described 499 patients who underwent SVP between 1990 and 2008, 14% of whom (72 of 499) had uAVSD.⁶ Children with uAVSD had worse overall survival and a higher risk of mortality after stage I and stage II procedures in univariable analysis. Rogers and coworkers⁷ reported 771 children who underwent Fontan palliation between 1992 and 2009, of whom 11.4% (88 of 771) had uAVSD. In multivariable analysis, uAVSD independently predicted death or Fontan takedown within 30 days of operation. Lee and colleagues⁸ reported 557 patients undergoing stage II palliation between 1998 and 2010, of whom 10.2% had uAVSD. They identified uAVSD as an independent risk factor for failure to achieve Fontan completion. Other recent large reports of Fontan outcomes did not analyze the impact of uAVSD on survival.^{9–14}

Overall, there is substantial mortality associated with uAVSD, much of which occurs in the first 5 years, so that only 66.5% of our patients were alive at 5 years after their first surgery, regardless of the stage of palliative procedure. After this, survival stabilized, with only a minor further decrease to 57.8% at 25 years. In our patients, aortic arch hypoplasia, and particularly aortic atresia, were independently associated with death or transplantation in multivariable analysis. In univariable analysis, the Norwood operation as the stage I procedure was associated with poorer outcomes, but this lost significance in the multivariable model. This likely occurred because the majority of these patients had aortic atresia or aortic arch hypoplasia, both of which are known risk factors for mortality following the Norwood procedure^{15,16} and were predictors of poor outcome in our multivariable model. Of further interest, LV hypoplasia itself was not associated with poor outcomes in our cohort. In large studies of SVP, hypoplastic left heart syndrome (HLHS) has been

associated with significantly poorer outcomes^{6,7,12}; however, in patients with hypoplastic LV with aortic atresia or arch hypoplasia, which are known to be higher-risk morphologies of HLHS,^{15,16} survival was indeed worse.

Another point of interest is the high rate of interstage mortality, with 11.7% of patients dying between stage I and stage II and 17.0% dying between stage II and Fontan. This is an interesting finding, considering that traditionally the majority of deaths have been thought to occur before BCPS.⁶ The age of our patients at Fontan operation was similar to that reported by other groups.^{6,9,14} Our previous results for the overall Fontan population,⁶ who were of a similar age as our uAVSD cohort, showed a much lower interstage mortality (just over 7% for both interstage periods). This finding suggests that the risk of interstage death may be specific to patients with uAVSD rather than to the age at which Fontan operation was performed. Furthermore, our findings are consistent with those of Lee and colleagues,⁸ who identified uAVSD as an independent risk factor for failure to progress from stage II palliation to Fontan.

Age at each stage of palliation decreased after the year 2000. After 2000, we tended to perform stage II palliation at the younger age of 3 months to try to minimize interstage mortality, as has been described previously.⁶ Other groups have shown that early BCPS is safe and have advocated its beneficial effects on pulmonary and coronary circulation and in reducing volume load on the systemic ventricle.^{17,18} We did not observe an improvement in survival over time; however, this may reflect the fact that patients with more complex disease underwent surgery in more recent years. For example, all Norwood procedures were performed after 2000, and these patients represent a particularly high-risk group.

Survival of our patients who achieved Fontan completion was 94.9% at 5 years and 82.4% at 25 years. These rates compare favorably with long-term survival in large outcome studies of the Fontan procedure, which reported 20-year survival of 71% to 77% in all patients after Fontan completion.^{6,11} Furthermore, cumulative freedom from death, Fontan takedown, or transplantation was 82.4% at 15 years after Fontan completion. This finding is consistent with results of recent studies of the entire Fontan population, which found 15-year freedom from Fontan failure in the range of 77% to 91%.^{10,12-14} In fact, this is slightly better than the results of the Fontan procedure in patients with HLHS, in whom we previously reported a 10-year freedom from failure of 79%.⁶ In addition, more than 80% of Fontan survivors were in NYHA functional class I at last follow-up. Hirsch and colleagues¹² also reported that approximately 80% of survivors in the general Fontan population were in NYHA class I. Thus, outcomes of patients with uAVSD who achieved Fontan completion are not different from those of the general population of patients with Fontan circulation. These results are in contrast to previous reports showing poor outcomes for patients with uAVSD undergoing Fontan.²⁻⁵

Heterotaxy has been previously described as a risk factor for the Fontan operation.^{9,19,20} Despite the associated challenges, there is evidence of recent improved outcomes in patients with heterotaxy syndrome undergoing the Fontan operation.^{20,21} The majority of our patients (73%; 102 of 139) had heterotaxy, making it difficult to assess the true impact of heterotaxy per se in patients with uAVSD. Because of the frequent association of heterotaxy and uAVSD, it has been suggested that these 2 factors may interact with each other on multiple regression analysis in these patients.⁸ Indeed, heterotaxy was not a risk factor for adverse outcomes in our patients, likely owing to the fact that the majority of our patients had this.

Surgery on the AVV was performed in nearly one-third of our patients. The operative mortality associated with the initial operation on the AVV was 18.2%, and another approximately one-third of patients underwent reoperation on the AVV. AVVR was previously identified as a risk factor for poor outcomes in SVP.^{2,6,22,23} Owens and coworkers³ reported that 30% of their uAVSD patients required operation for AVVR. They identified undergoing an operation on the AVV as a significant risk factor for death, with 75% of patients who underwent an AVV operation deceased at a mean follow-up of 25 months. In our cohort, significant AVVR before initial palliation was associated with poorer long-term outcomes. Conversely, significant AVVR at the time of stage II palliation was associated with early death, but not with poorer long-term survival.

This may reflect the fact that few AVV repairs were performed at stage I, when unrepaired AVVR may contribute to late death. Surgery for AVVR was commonly performed at stage II, which might increase surgical risk but may mitigate the risk of late death. These findings are consistent with previous reports indicating that AVVR is a significant risk factor for poor outcomes following stage II.^{8,24} In fact, it has been shown that failure to achieve a successful repair of an AVV with significant regurgitation at the time of stage II is associated with mortality.⁸ In our patients, it appears that the AVV of those who survived to Fontan completion was of better quality, as demonstrated by a lower rate of AVV operations (Figure 3, A). Moreover, it was uncommon for patients to require an AVV operation following Fontan completion (Figure 3, B). Taken together, the foregoing findings emphasize the importance of a competent AVV in patients with uAVSD; however, for those patients with uAVSD and significant AVVR, achieving such competence is particularly challenging.

Unfortunately, simple annuloplasty and “edge-to-edge” repair are often unreliable.^{25,26} In an attempt to address this issue, our group has adopted the “bridging technique” for AVV repair in children with a single ventricle, as described previously.²⁶⁻²⁸ This technique has shown promising early results, but its long-term outcomes remain to be established.²⁵ We are hopeful that this technique can reduce some of the burden associated with AVVR in this cohort.

This study is limited by its retrospective nature. Although this is the largest study of patients with uAVSD who underwent SVP reported to date, our relatively limited sample size precluded further detailed analysis. This might have affected our ability to demonstrate the significance of some postulated risk factors.

CONCLUSIONS

Children with uAVSD undergoing univentricular repair have high mortality, with <60% of patients alive at 25 years after initial palliation. Furthermore, AVVR is a major problem in this group, with nearly one-third of patients requiring AVV surgery, of whom a further one-third required AVV reoperations. However, survival of patients who achieve Fontan completion is better than has been reported previously, and not different from that in the general Fontan population.

Conflict of Interest Statement

Dr d’Udekem is a consultant for MSD and Actelion. Dr Brizard serves on the advisory board of Admedus. Dr Weintraub serves on the advisory board of Actelion. All other authors have nothing to disclose with regard to commercial support.

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