Effect of Earlier Atrioventricular Valve Intervention on Survival After the Fontan Operation

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Whereas the prevalence and impact of atrioventricular valve (AVV) regurgitation in patients with single ventricle physiology has become increasingly apparent, the optimal timing for valve intervention is unclear. To investigate this, we performed a retrospective review of all 1,167 patients from the Mayo Clinic Fontan database. Thirteen percent (153 patients) had AVV repair or replacement during their staged single ventricle palliation. We found that patients with right ventricular morphology and common AVV were at increased risk for AVV intervention. Patients who underwent AVV intervention had increased risk of death/transplant compared with those who did not (hazards ratio [HR] = 1.75, 95% CI 1.37 to 2.23, p <0.001). With respect to valve intervention timing, whereas AVV intervention before Fontan presented similar risk for death/transplant compared with no AVV intervention (HR = 0.85, 95% CI 0.32 to 2.27, p = 0.74), intervention *at time* of Fontan had a significantly higher risk (HR = 1.46, 95% CI 1.09 to 1.97, p = 0.01), and intervention *after* Fontan had a much more substantial risk (HR = 3.83, 95% CI 2.54 to 5.79, p <0.001). AVV repair failure occurred in 11% of patients. In terms of relative risk of valve repair versus replacement, in post-Fontan AVV intervention patients, AVV replacement carried a 2.9 fold risk of death/transplant compared with AVV repair. In conclusion, AVV disease remains a considerable challenge for durable Fontan physiology. This data demonstrates that earlier intervention on valve pathology improves survival with the Fontan circulation. Continued surveillance of single ventricle patients and prompt referral of those with valve pathology can improve outcomes in this challenging population. **(Am J Cardiol 2020;137:103−110)**

A competent atrioventricular valve (AVV) is one of the tenants of a successful Fontan circulation. In 1977 Choussat and Fontan noted that more than mild AVV regurgitation adversely impacted outcomes.[1] The prevalence and impact of AVV pathology has become increasingly apparent, with studies from the Australia and New Zealand Fontan Registry highlighting the association of AVV failure with Fontan failure.[2,3] However, the optimal timing of AVV intervention remains unknown. Since 1973, Mayo Clinic has maintained a comprehensive database of patients who had a Fontan operation with long-term follow-up.[4] This database provides a unique opportunity to examine the role of timing of AVV repair and replacement on outcomes. Such analysis can provide insight into the appropriate timing of referral for AVV intervention, and thereby improve outcomes for these challenging patients.

Methods

A retrospective review was performed of all patients in the Mayo Clinic Fontan database from January 1973 to February 2019. Permission was granted by the Institutional Review Board to perform this study. Data gathered included standard demographics, underlying anatomy, operative details, timing of first AVV intervention relative to Fontan, as well as long-term follow-up. Fontan connection type was based on the first Fontan operation in cases when patients underwent multiple Fontan revisions. Analyses were based on the first AVV interventions, although follow-up data were acquired relative to subsequent valve interventions and outcomes. For the AVV repair cohort, one of the primary end-points was reintervention on the valve, with echocardiographic outcomes as a secondary end-point. Echocardiographic follow-up data were obtained from the most recent echocardiogram, or the last study before heart transplantation or death, if applicable.

Statistical analysis was performed with the primary end point of survival with Fontan. Transplant and death from any cause were censored. Given the time-dependent nature of the data, Cox proportional hazards analysis with time-dependent variables was determined to be the most appropriate method for statistical analysis. Of note, this type of analysis does yield visual representation of risk or outcome over time. Cox proportional hazards analysis was performed using Stata, version 14 with time dependent variables when appropriate. Analysis was adjusted for age and sex. Cross tab and descriptive analysis was performed using SPSS version 25 (IBM, Chicago, IL). Data are reported as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data.

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Results

Of the 1,167 patients in the database, 153 (13%) required AVV intervention throughout the stages of single ventricle palliation. Compared with patients who did not receive AVV intervention, those having intervention were more likely to have heterotaxy and unbalanced atrioventricular septal defect, but less likely to have double inlet left ventricle (Table 1). Those requiring AVV intervention were more likely to have a dominant right ventricle, a common AVV (CAVV), and less likely to have a morphologic mitral valve. In terms of Fontan connection type, those requiring valve interventions were more likely to have a lateral tunnel and less likely to have an atriopulmonary connection. There was no difference between eras of the Fontan operation and need for valve intervention.

In terms of timing of valve intervention, the median age at first valve intervention was 9 (12) years (Table 2). Eleven percent of the 158 patients had their first valve intervention pre-Fontan, 63% at Fontan, and 25% post-Fontan. The vast majority had a repair as their first intervention (81%), and AVV repair was most frequent in the CAVV group (92%). The majority of the post-Fontan AVV interventions were in morphologic mitral valves, whereas CAVV formed the majority of the pre-Fontan AVV interventions. Patients with AVV intervention at time of Fontan completion had less regurgitation than those who had intervention pre-Fontan and post-Fontan and the post-Fontan group had the lowest ejection fraction.

Valve morphology was related to risk for needing repair. Patients with CAVV were more likely to undergo intervention earlier in the staged palliation process with only 11% undergoing first AVV intervention post-Fontan (Table 3). Patients with morphologic mitral valve were substantially more likely to undergo AVV intervention later with 42% having their first intervention post-Fontan. Patients with CAVV were most likely to undergo valve repair (92%) and had an 18% incidence of valve repair failure, which was quantitatively higher than patients with mitral or tricuspid morphologies (8% and 4%, respectively), but this was not statistically significant likely due to the small number of events (p = 0.1).

Table 1
Patients with and without atrioventricular valve intervention

Variable	Total cohort (n = 1,167)	No valve intervention (n = 1,014)	Valve intervention (n = 153)	p Value
Age at Fontan (years)	7.5 (9.6)	7.4 (8.8)	7.6 (9.6)	0.654
Men	700 (60%)	616 (61%)	84 (55%)	0.233
Heterotaxy				
Asplenia	77 (7%)	51 (5%)*	26 (17%)*	<0.001
Polysplenia	63 (5%)	42 (4%)*	21 (14%)*	<0.001
Underlying anatomy				<0.001
DILV	302 (26%)	283 (28%)*	19 (12%)*	
DIRV	23 (2%)	19 (2%)	4 (3%)	
DORV	7 (1%)	7 (1%)	0 (0%)	
DORV-TGA	100 (9%)	86 (9%)	14 (9%)	
HLHS	33 (3%)	32 (3%)	1 (1%)	
MA	48 (4%)	41 (4%)	7 (5%)	
Other	70 (6%)	59 (6%)	11 (7%)	
PA-IVS	61 (5%)	58 (6%)	3 (2%)	
TA	317 (27%)	285 (28%)	32 (21%)	
UAVC	147 (13%)	93 (9%)*	54 (35%)*	
UHAVV	51 (4%)	43 (4%)	8 (5%)	
Dominant ventricle				<0.001
Left	791 (69%)	722 (73%)*	69 (47%)*	
Right	351 (31%)	272 (27%)*	79 (53%)*	
Valve morphology				<0.001
MV	673 (66%)	620 (70%)*	53 (38%)*	
TV	200 (20%)	174 (20%)	26 (18%)	
CAVV	154 (15%)	92 (10%)*	62 (44%)*	
Glenn	208 (19%)	176 (19%)	32 (22%)	0.206
Fontan type				<0.001
AP	625 (54%)	561 (55%)*	64 (42%)*	
Lateral Tunnel	291 (25%)	229 (23%)*	62 (41%)*	
Extracardiac	151 (13%)	130 (13%)	21 (14%)	
Fenestration	118 (11%)	99 (11%)	19 (13%)	0.251
Era				0.97
1973-1989	742 (64%)	644 (64%)	98 (64%)	
1990-2000	265 (23%)	230 (23%)	35 (23%)	
2000-2019	160 (14%)	140 (14%)	20 (13%)	

Non-normally distributed data is presented as median (Interquartile range). DILV = double inlet left ventricle; DIRV = double inlet right ventricle; DORV = double outlet right ventricle; TGA = transposition of the great arteries; HLHS = hypoplastic left heart syndrome; MA = mitral atresia; PA-IVS = pulmonary atresia intact ventricular septum; TA = tricuspid atresia; UAVC = unbalanced atrioventricular canal; UHAVV = univentricular heart atrioventricular valve; MV = mitral valve; TV = tricuspid valve; CAVV = common atrioventricular valve. AP = atriopulmonary.

Table 2
Timing of valve intervention

Variable	Total cohort (n = 153)	Pre-Fontan (n = 17, 11%)	At Fontan (n = 97,63%)	Post-Fontan (n = 39, 25%)	p Value
Age (years) at first AVV intervention	9.0 (12.1)	2.3 (5.0)	8.6 (9.7)	18.0 (11.8)	<0.001
Men	77 (55%)	6 (35%)	55 (67%)	23 (59%)	0.22
Heterotaxy					
Asplenia	22 (16%)	4 (24%)	19 (20%)	3 (8%)	0.203
Polysplenia	20 (15%)	2 (12%)	16 (17%)	3 (8%)	0.402
Glenn**	29 (22%)	13 (77%)	16 (17%)	3 (8%)	<0.001
Fontan type					<0.001
Atriopulmonary	61 (44%)	1 (6%)^*	42 (43%)*	21 (54%)^	
Lateral Tunnel	57 (41%)	9 (53%)	43 (44%)	10 (26%)	
Extracardiac	17 (12%)	6 (35%)*	12 (12%)	3 (8%)*	
Kawashima	17 (12%)	2 (12%)	14 (14%)	2 (5%)	0.333
Fenestration	16 (12%)	7 (41%)^*	9 (10%)*	3 (8%)^	0.001
Era					<0.001
1973-1989	91 (65%)	3 (18%)^*	66 (68%)*	29 (74%)^	
1990-2000	32 (23%)	5 (29%)	25 (26%)	5 (13%)	
2001-2019	17 (12%)	9 (53%)^*	6 (6%)*	5 (13%)^	
Valve morphology					0.004
Mitral valve	53 (38%)	5 (33%)	26 (29%)*	22 (61%)*	
Tricuspid valve	25 (18%)	1 (7%)	17 (19%)	7 (19%)	
Common AVV	62 (44%)	9 (60%)*	46 (52%)^	7 (19%)^*	
Ventricular Dominance					0.002
Left Ventricle	70 (47%)	10 (59%)	36 (39%)*	24 (63%)*	
Right Ventricle	78 (53%)	7 (41%)	57 (61%)*	14 (37%)*	
Pre-Repair					
Ejection Fraction (%)	50 (11)	55 (14)	53 (10)	45 (10)	<0.001
Degree of regurgitation#	2 (1)	3 (1)	2 (1)	3 (1)	<0.001
First AVV intervention					
Repair	114 (81%)	13 (77%)*	94 (97%)^*	17 (44%)^	<0.001
Annular	96 (69%)	13 (77%)	69 (71%)	23 (59%)	0.293
Leaflet	25 (18%)	3 (19%)	16 (17%)	9 (23%)	0.669
Subvalvar	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.752
Replacement	26 (19%)	4 (24%)*	3 (3%)^*	22 (56%)^	<0.001
Bioprosthetic	3 (2%)	1 (6%)*	0 (0%)^*	3 (8%)^	
Mechanical	20 (14%)	2 (12%)*	2 (2%)^	18 (47%)^*	
Operative mortality	22 (16%)	0 (0%)	18 (19%)	5 (13%)	0.124
Valve Repair					
Valve repair failure	16 (11%)	7 (41%)^*	6 (6%)^	3 (8%)*	<0.001
Time to valve repair failure (months)	17 (52)	11 (28)	68 (123)	11	0.086
Echo s/p Valve Repair					
Years after repair	6.0 (14.6)	4.7 (12.5)	6.0 (17.2)	6.3 (10.0)	0.975
Degree of regurgitation#	1 (1.8)	1 (1)	1 (1.5)	0 (0.5)	0.005
Ejection fraction (%)	50 (12)	50 (21)	48 (15)	50 (10)	0.56
Follow-up after Fontan (years)	14.2 (21.9)	10.0 (16.5)	11.2 (22.5)	19.2(23.5)	0.036
Transplant-free Survival	73 (48%)	13 (77%)*	48 (50%)	12 (31%)*	0.006

Non-normally distributed data is presented as median (Interquartile range). **Refers to Glenn as part of the patient's palliative staging, not necessarily that Glenn was performed before valve work in the Pre-Fontan group.

AVV = atrioventricular valve; s/p = status post.

1= Mild, 2 = Moderate, 3 = Severe.

Valve repair operative details were available for 112 of 114 patients who had AVV repair as their first intervention (Table 2). Of these, 96 (69%) had annular interventions and 25 patients (18%) had leaflet interventions, with details provided in Table 2. Only 1 patient (1%) had subvalvar intervention. Among the 26 patients who had valve replacement, the vast majority (20) had mechanical valve replacements.

Many patients in the pre-Fontan group underwent multiple valve repairs early during staged palliation (pre-Fontan and at Fontan), but no further valve interventions post-Fontan. All except 2 of the patients in the pre-Fontan repair group retained their native valve (Figure 1). For example, of the 5 patients who had pre-Glenn AVV repair, 2 had a subsequent pre-Glenn AVV repair, 1 had a post-Glenn repair, 1 had valve repair at time of Fontan, and 1 required replacement at time of Fontan. Of the 5 patients whose first AVV repair was at the Glenn, 1 underwent post-Glenn repair and no further interventions, and 1 underwent post-Glenn replacement. Notably, this pre-Fontan group also had the highest transplant-free survival.

Table 3
Valve morphology in patients undergoing valve intervention

Variable	Total cohort (n = 153)	MV (n = 53)	TV (n = 25)	CAVV (n = 62)	p Value
Age (years) at first AVV intervention	9.0 (12.1)	10.5(17.3)	12.1(13.1)	8.0 (9.5)	0.475
Men	77 (55%)	33 (62%)	12 (48%)	32 (52%)	0.384
Heterotaxy					
Asplenia	22 (16%)	0 (0%)*	2 (8%)	20 (32%)*	<0.001
Polysplenia	20 (15%)	1 (2%)^*	6 (25%)^	13 (21%)*	0.004
Glenn	29 (22%)	7 (14%)	4 (17%)	18 (30%)	0.115
Fontan type					<0.001
Atriopulmonary	61 (44%)	34 (64%)*	12 (48%)	15 (24%)*	
Lateral Tunnel	57 (41%)	10 (19%)*	9 (36%)	38 (61%)*	
Extracardiac	17 (12%)	4 (8%)	4 (16%)	9 (15%)	
Kawashima	17 (12%)	1 (2%)	4 (16%)	12 (19%)	0.014
Fenestration	16 (12%)	3 (6%)	2 (8%)	11 (8%)	0.11
Era					0.705
1973-1989	91 (65%)	35 (66%)	19 (76%)	37 (60%)	
1990-2000	32 (23%)	12 (23%)	4 (16%)	16 (26%)	
2000-2019	17 (12%)	6 (11%)	2 (8%)	9 (15%)	
Timing of first valve work					0.002
Pre-Fontan	15 (11%)	5 (9%)	1 (4%)	9 (15%)	
Fontan	89 (64%)	26 (49%)*	17 (68%)	46 (74%)*	
Post-Fontan	36 (26%)	22 (42%)*	7 (28%)	7 (11%)*	
Pre-Repair					
Ejection Fraction %	50 (11)	52 (14)	55 (19)	50 (10)	0.597
Degree of regurgitation#	2 (1)	2 (1)	2 (1)	2 (0)	0.01
First AVV Intervention					0.016
Repair	114 (81%)	38 (72%)*	19 (76%)	57 (92%)*	
Annular	96 (69%)	33 (62%)	15 (60%)	48 (74%)	0.13
Leaflet	25 (18%)	9 (17%)	2 (8%)	14 (23%)	0.273
Subvalvar	1 (1%)	0 (0%)	1 (4%)	0 (0%)	0.597
Replacement	26 (19%)	15 (28%)*	6 (24%)	5 (8%)*	0.372
Bioprosthetic	3 (2%)	1 (2%)	1 (4%)	1 (2%)	
Mechanical	20 (14%)	5 (11%)	4 (16%)	3 (5%)	
Operative mortality	22 (16%)	7 (13%)	4 (16%)	11 (18%)	0.78
Valve Repair					
Valve repair failure	16 (11%)	4 (8%)	1 (4%)	11 (18%)	0.101
Time to valve repair failure (months)	17 (52)	11		27 (53)	0.989
Echo s/p Valve Repair					
Years after repair	6.0 (14.6)	10.0(16.7)	4.1 (13.9)	5.8 (13.2)	0.191
Degree of regurgitation#	1 (1.8)	1 (1)	0.5 (1)	1 (2)	0.287
Ejection fraction	50 (12)	50 (12)	48 (21)	45 (13)	0.058
Follow-up after Fontan (years)	14.2 (21.9)	16.3(21.5)	18.6(24.8)	12.7(22.1)	0.495
Transplant-free Survival	73 (48%)	22 (42%)	12 (48%)	32 (52%)	0.554

Non-normally distributed data is presented as median (Interquartile range).
MV = mitral valve; TV = tricuspid valve; CAVV = common atrioventricular valve. s/p = status post; AVV = atrioventricular valve.
Note: 13 patients were not within MV, TV or CAVV categories or were unknown. #1 = mild, 2 = moderate, 3 = severe.

To determine if an era effect existed, patients were assessed during 3 time periods of surgery: "Early Era" from 1973 to 1989, "Middle Era" from 1990 to 2000 and a "Recent Era" from 2001 to 2019. Analysis found that the rate of valve repair varied across eras (p = 0.02): patients in the Early Era (<1990) were less likely to undergo valve repair as the first intervention (75% repair and 25% replacement), compared with the Middle Era at 94% repair rate, which was not statistically significantly different than the Recent Era (90%). Timing of first valve intervention also varied with era (p <0.001) with pre-Fontan intervention occurring more commonly in the Recent Era (45%), compared with the Early Era (3%) or Middle Era (14%, all p <0.05 on post-hoc testing). First valve intervention at time of Fontan was more common in the Early and Middle Eras (67% and 71%) compared with the Recent Era (30%, p <0.05 on post-hoc testing). Correspondingly, patients were older at first valve intervention in the Early Era compared with the Middle and Recent Eras (12 [12] years, vs 6 [8] years and 5 [17] years in the Middle and Recent eras, respectively). Interestingly, whereas operative mortality was quantitatively higher in the Early Era (19%), it was not statistically significantly different than the later eras (9% and 10%, Middle and Recent Era, respectively, p = 0.29). Degree of regurgitation preoperatively was not statistically different between eras, but ejection fraction was lowest in the Early Era (median 50 [15]%, compared with 56 [11]% and 55 [13%] in the Middle and Recent Eras, respectively).

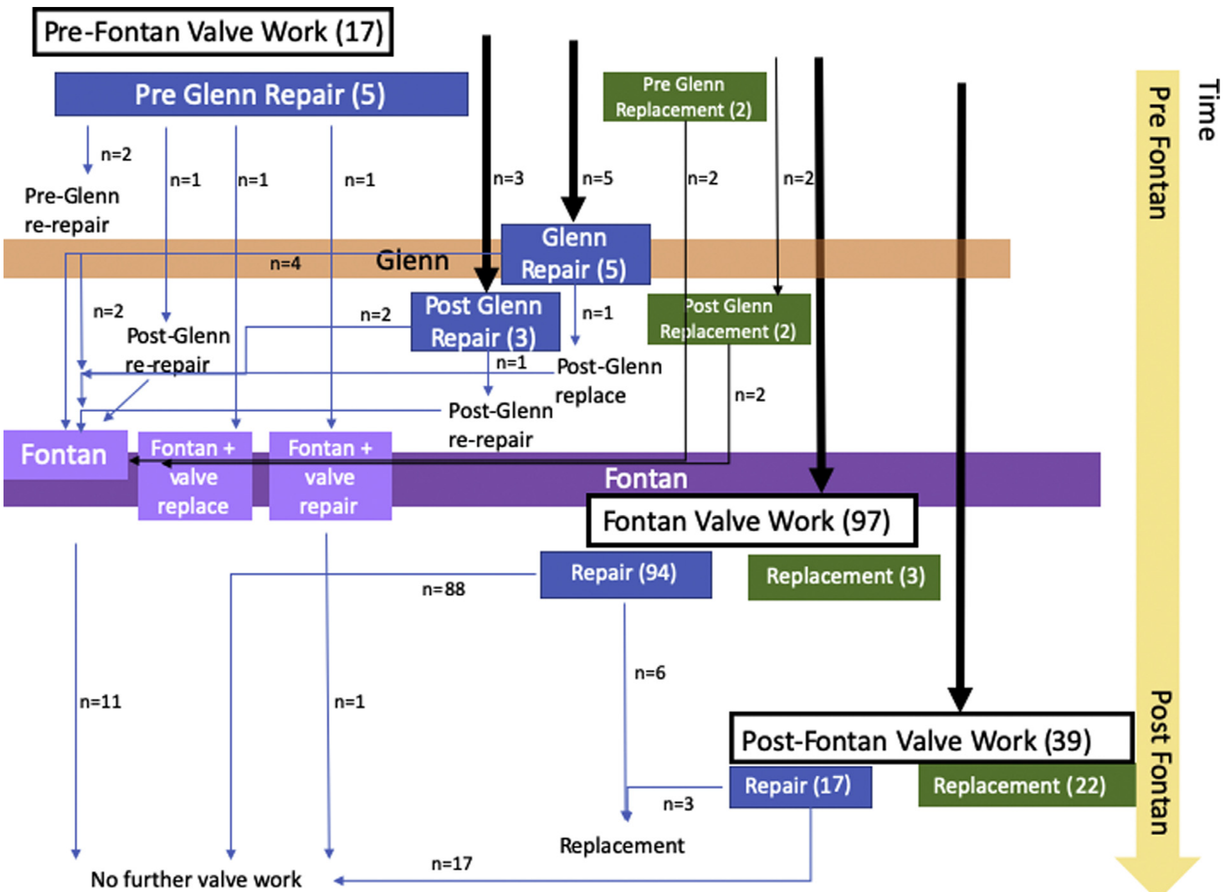

Figure 1. Diagrammatic flow sheet for the patients who underwent atrioventricular valve intervention. For patients who underwent pre-Fontan atrioventricular valve intervention, timing of intervention(s) is demonstrated relative to Glenn (if applicable). The number of patients within each pathway are represented with ("n=").

As expected, type of Fontan connection varied by era with extracardiac conduits exclusively performed in the Middle and Recent Eras, and atriopulmonary Fontan almost exclusively in the Early Era. Age at Fontan also decreased with era: 9 (10) years in Early Era, 6 (7) years in Middle, and 5 (4) years in Recent, p <0.001. The distributions of anatomy, valve morphology, and ventricular dominance were similar across eras. Valve replacement as the first AVV intervention in the pre-Fontan group exclusively occurred before 1985.

With regards to early outcomes, the overall early mortality was 16% across the cohort; it was 22% in the earliest era and 10% across the last 2 eras (Table 2). Early mortality was 0% in the pre-Fontan AVV intervention group. There was no difference in early mortality among valve morphology. Whereas the early mortality was quantitatively higher in the Fontan and post-Fontan AVV intervention groups (19% and 13%, respectively, vs 0% in pre-Fontan group) this did not reach statistical significance with a small number of events (p = 0.124). In the current era, early mortality for initial modified Fontan is less than 3% and for Fontan revision is less than 5%.

Long-term outcomes, specifically transplant-free survival, were analyzed for patients with and without valve intervention using time-dependent Cox proportional hazards model. After adjusting for sex and age at time of Fontan, those who underwent valve intervention were at higher risk for death or transplant than those who did not (hazards ratio [HR] = 1.75, 95% CI 1.37 to 2.23, p <0.001). When timing of valve intervention was analyzed, the pre-Fontan group was not at increased risk for death or transplant compared with those who did not require intervention (HR = 0.85, 95% CI 0.32 to 2.27, p = 0.74). In contrast, those who underwent valve intervention *at the time of* Fontan had a significantly higher risk of death or transplant than those who did not require intervention (HR = 1.46, 95% CI 1.09 to 1.97, p = 0.01) and the post-Fontan group had an even more substantial risk of death or transplant compared with those who did not require valve surgery (HR = 3.83, 95% CI 2.54 to 5.79, p <0.001).

Additional analysis was performed on patients who underwent valve repair. Those who underwent valve repair before Fontan were at significantly higher risk of valve repair failure than those who had valve repair at the time of Fontan (HR = 19.31, 95% CI 5.33 to 70.10, p <0.001). The rate of valve repair failure was 11% across the cohort, including 54% (7 of 13) in the patients who needed repair before Fontan compared with 6% (6/95) for those who had repair at time of Fontan. Patients who underwent valve repair after Fontan showed a trend of

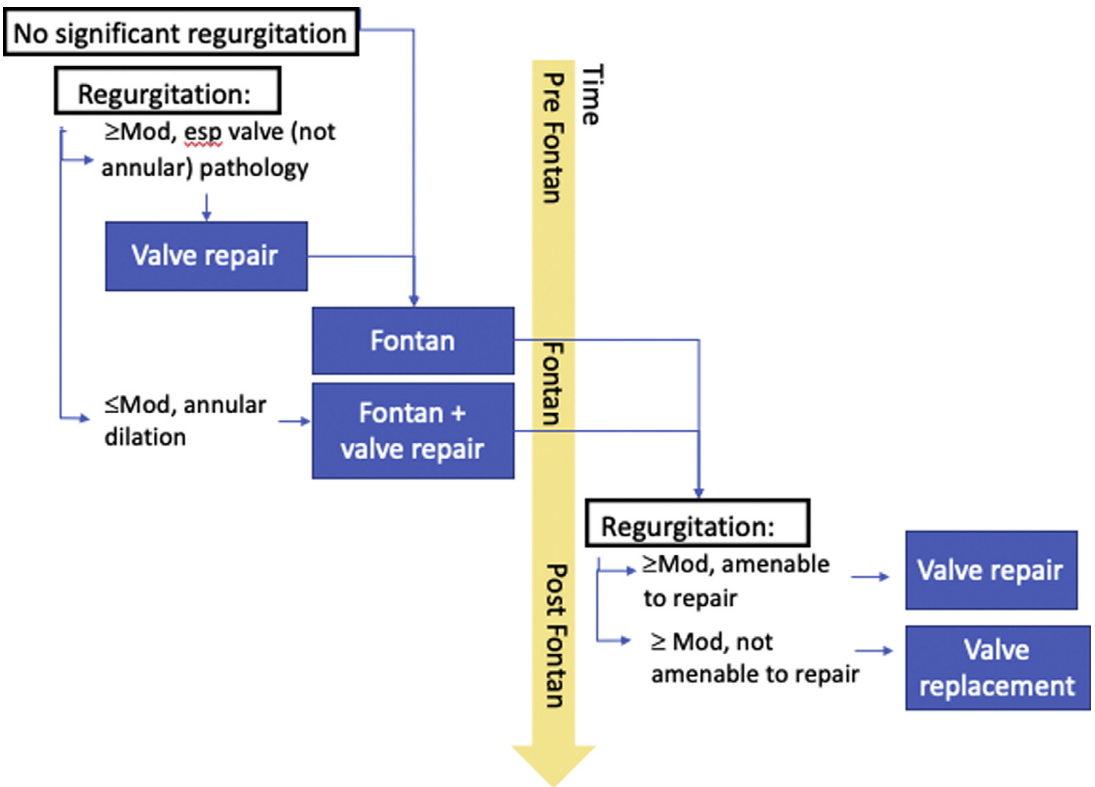

Figure 2. Proposed algorithm for the surgical management of atrioventricular valve regurgitation in patients with single ventricle physiology. Mod = moderate, esp = especially. Each patient must be considered individually and this algorithm simply acts as a guideline. The emphasis should be on preserving ventricular function and once moderate regurgitation has developed especially when ventricular dilation is present, consideration should be made for valve intervention. Clinical status and symptoms should be taken into account. Symptoms can be difficult to assess in children, but rising diuretic requirement and increasing afterload-reducing agents are warning signs (See also discussion in Stephens and Dearani).[18]

increased risk of valve repair failure compared with those who had valve repair at time of Fontan (HR = 3.88, 95% CI 0.89 to 16.89, p = 0.07). Patients who required valve intervention after the Fontan palliation were analyzed to compare survival in those patients that had valve repair versus those that underwent valve replacement. Patients with valve repair demonstrated a survival benefit compared with those who underwent valve replacement (HR = 0.35, 95% CI 0.14 to 0.85, p = 0.02). Those with valve replacement after Fontan had a 2.9 times higher risk of death or transplant compared with those who had valve repair. Analysis was performed to determine whether the variables valve type, type of ventricle, or type of Fontan effected the regression, but none of these were found to be statistically significant (p = 0.75, p = 0.94, and p = 0.08, respectively).

Echocardiographic follow-up was available for 60 of the 117 patients who had valve repair and did not undergo subsequent valve replacement. Analysis of these data revealed that at a median follow-up of 6 (15) years the median degree of regurgitation for the repaired valve was mild with a median ejection fraction of 50% (12%). The ejection fraction tended to be highest in the morphologic mitral valve group (50% [12%]) and lowest in the CAVV group (45% [13%], p = 0.058). Duration of echocardiographic follow-up and regurgitation grade were not different between groups.

Discussion

The present study expands our knowledge of AVV disease in Fontan patients by examining the impact of *timing* of AVV intervention on outcomes. Similar to previous studies, we demonstrated a substantially increased risk of transplant and death among patients who undergo AVV intervention,[2,5] with patients having a dominant right ventricle and CAVV at greatest risk for requiring AVV intervention. Importantly, whereas patients who had their first AVV intervention before Fontan were not at increased risk of mortality or transplant relative to those who never required AVV intervention, those who had their first AVV intervention a*t Fontan* demonstrated increased risk (HR 1.46), and those who had their first valve intervention *after Fontan* demonstrated a substantially higher risk (HR 3.83). Analysis of patients undergoing their first valve intervention after Fontan revealed those who underwent repair fared better than valve replacement. Based on these data and our experience in this area, we have developed an algorithm for AVV intervention, intended to be applied in the context of each individual patient's anatomy and clinical condition (Figure 2). Whereas medical management of valve regurgitation in Fontan patients is discussed in guidelines, surgical management is not.[6]

The role of AVV disease on Fontan outcomes was recently highlighted in a study of 120 patients from the

Australia and New Zealand Fontan Registry who underwent AVV intervention, with 103 undergoing valve intervention at or pre-Fontan.[2] Importantly valve failure, defined as either moderate or greater regurgitation or need for valve intervention, was common (1/3 at 10 years and ½ at 20 years) and was strongly associated with adverse outcomes. A subset analysis demonstrated that patients undergoing tricuspid valve repair were at particular risk for valve repair failure and poor outcomes.[3] In the present study we have expanded the field's knowledge on this topic by investigating the role of *timing* of AVV intervention on outcome. Our single institution Fontan experience has different characteristics compared with the Australia and New Zealand Fontan Registry, adding further insight. Most notably, the underlying diagnoses are broader and include substantially more heterotaxy syndrome patients (31% vs 8%).[2]

The challenges of a durable AVV repair in single ventricle physiology are becoming increasingly recognized. Whereas morphologic mitral valves appear to have more durable results in the biventricular circulation,[7,8] and in Fontan patients,[2] repair of the CAVV in unbalanced atrioventricular septal defect has proven more difficult in patients with functional single ventricle physiology,[2,9] and has been identified as a risk factor for mortality and attrition before Fontan completion.[10−12] Morphologic tricuspid valves have also proven to be more difficult to repair and progressive regurgitation is associated with Fontan failure.[2,13,14] Whereas valve repair has demonstrated mixed results,[13,15] a successful, durable valve repair can dramatically improve outcome when it can be achieved.[16,17] In our study, the valve repair failure rate (11%) was significantly less than noted in the Australia and New Zealand registry (32% at 5 years), and was 18% in CAVV, 4% in tricuspid and 8% in mitral valve patients. There was a 41% AVV repair failure rate among those who had repair before Fontan, reflecting challenging valve pathology and in part was a programmatic decision as we recognize that severe regurgitation would be a strong risk factor for mortality if addressed at the same time as Fontan. Whereas many patients in the pre-Fontan AVV intervention group had multiple early valve re-repairs, the majority retained their valve without requiring valve interventions post-Fontan, and demonstrated the highest transplant-free survival.

The data in the present study confirm concepts recently discussed;[18] specifically the role of valve and ventricular morphology in the outcomes of valve repair for patients with functional single ventricle physiology. When the right ventricle, designed to provide output to a low resistance pulmonary bed, is tasked with providing output to the higher afterload systemic circulation, it is not surprising that these ventricles are at risk for progressive systolic failure. With progressive dilation, the annular and ventricular geometry changes predisposing the valve to develop regurgitation. Tricuspid valve and CAVV morphologies present challenging substrates for repair, and even when leaflet and annular issues can be addressed, often subvalvar and ventricular size and geometry issues that contribute to progressive regurgitation are not addressed. Given concerns regarding valve repair durability among certain patients, the question becomes whether replacement might improve outcomes as recurrent regurgitation is prevented allowing sustained ventricular remodeling. Analysis of the patients who underwent valve intervention after Fontan found a survival advantage to repair. These data, however, include a selection bias: patients who underwent valve replacement were likely patients in whom a durable repair was doubtful.

The data in this study demonstrate a substantially increased risk of mortality or need for cardiac transplant among patients who underwent valve intervention *after* Fontan, in spite of the likely selection bias of these patients who had "better" valves (i.e., did not require intervention until later). This group had the lowest ejection fraction predisposing them to worse outcomes and may reflect a population in whom the intervention was too late. These data support early, proactive intervention on the valve before declining ventricular function, including adding a staged operation before the Fontan when appropriate (Figure 2).[18] Providing early valve competence and preserving ventricular function are essential. The careful surveillance by cardiologists and primary care providers of this at risk population and prompt referral of patients to centers experienced with valve repair in single ventricle patients remain critical in optimizing outcomes.

Inherent limitations based on study design and cohort include the study's single center retrospective nature and the selection bias for repair versus replacement. Additionally, timing of the valve intervention was not governed by particular guidelines and may have varied among surgeons and referring cardiologists. The design of the study allows demonstration of associations, and while the findings are striking, does not enable analysis of causation. Although this series spans 5 decades, including changes in the predominant Fontan connection techniques, there were no detectable differences in the incidence of valve intervention between eras. The distribution of single ventricle anatomy in this cohort of patients may be different than that seen at other institutions, particularly the relatively low numbers of patients with hypoplastic left heart syndrome and high number with heterotaxy. Patients who underwent valve interventions and portions of their Fontan palliation at other institutions were included in order to maximize the statistical power, but does present the potential for immortal time bias; however, this was a very small number of patients. Late echocardiographic data are somewhat limited, but the primary endpoint for the valve repair group was reintervention on the valve, not the degree of regurgitation. Whereas many patients in this study are followed at other institutions, serial surveys and continued communication between home physicians and our institution were maximized so accurate and current clinical follow-up was available with minimal gaps in data acquisition. There may also be patients with significant AVV regurgitation who were not deemed surgical candidates and are not reflected in this cohort.

In conclusion, AVV disease remains a considerable challenge and compromises Fontan durability. In this study we demonstrate the importance of earlier AVV intervention, and prefer valve repair when feasible, to improve outcomes in the Fontan circulation. These data emphasize the continued surveillance by cardiologists and primary care providers of this at risk population, and prompt referral of patients to centers experienced in valve repair in this population.

Credit Author Statement

Stephens: Conceptualization, Methodology, Investigation, Formal Analysis, Writing (original draft, Review/editing).

Dearani: Conceptualization, Writing (Review/Editing).

Niaz: Conceptualization, Investigation.

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Phillips: Investigation, Writing (Review/Editing).

Cetta: Conceptualization, Methodology, Investigation, Writing (original draft, Review/editing).

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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