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ORIGINAL ARTICLE

What Factors Predict Long-Term Survival and Valve Durability in Patients With Atrioventricular Valve Regurgitation in Single-Ventricle Physiology?

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Abstract Although significant atrioventricular valve regurgitation (AVVR) is well known for its association with increased morbidity and mortality in patients with single-ventricle physiology, there is a lack of consensus in management of AVVR. The purpose of this study was to analyze the clinical outcomes in patients receiving AVV repair or replacement. From 2001 to 2010, a total of 33 patients (25 male and 8 female) with more than moderate-degree AVVR among 160 patients who underwent staged single-ventricle palliation were included. The median follow-up duration was 6.0 years (range 0.1–14.1). Valve repair ($n = 27$) or valve replacement ($n = 6$) was performed at the initial surgery. There were six late mortalities (18.18 %): five in the repair group and one in the replacement group and seven morbidities. Among patients with valve repair, 11 were required to undergo redo-valve operations (valve repair $n = 6$, valve replacement $n = 5$) due to deteriorated valve function. Initial shunt procedure ($p = 0.04$) and arrhythmia ($p = 0.01$) were risk factors for survival. Freedom from reoperation in the valve replacement group was higher than that in the valve repair group (67.0 ± 9.7 and 44.6 ± 11.2 % at 5 and 6 years, respectively, $p = 0.03$). Need for early repair ($p = 0.02$), presence of mitral- or tricuspid-dominant AVV ($p = 0.005$), and male sex ($p = 0.04$) were risk factors for valve durability. Early valve regurgitation affects valve durability. Thus, successful repair in the early stage may improve later outcomes. Therefore, aggressive valve surgery was required and AVV replacement might be one of the options for selected patients.

Keywords Atrioventricular valve regurgitation · Single ventricle · Valve replacement · Heterotaxy syndromes

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Introduction

Significant atrioventricular valve regurgitation (AVVR) is well known for its association with increased morbidity and mortality in patients with a single-ventricle physiology [4, 10]. Although the cause of AVVR has not been clearly established, two main hypotheses have been raised. Chronic volume overload due to a systemic-pulmonary shunt with subsequent ventricular dilatation and AV annular dilatation has been considered as one cause [14]. Mahle et al. [15] proposed that a bidirectional cavopulmonary connection is one of the optimal treatment options for AVVR by decreasing shunt flow. However, this clinical study showed the only 22 % of patients had improved valve regurgitation at the time of bilateral cavopulmonary shunt (BCPS). In contrast, morphologic abnormality of the AV valve is also known to be a major contributor to AVVR [1, 9]. Honjo et al. [9] reported that anatomical AV repair in the early stage had more favorable outcomes. The treatment strategy in our institution was also to perform AV valve repair or replacement for patients with more than moderate-degree AVVR. However, we observed that late clinical deteriorations of AV valve function occurred in some patients who had successful immediate results from AV valve repair. Thus, the purpose of this study was to analyze the risk

factors of late clinical deterioration and surgical outcomes of AV valve surgery.

Materials and Methods

The study protocol was approved by the Institutional Review Board of the University of Seoul National University Hospital (no. H-1107-003-366), and the procedures were conducted in accordance with institutional guidelines for the protection of patient confidentiality. The need for consent was waived due to the retrospective study design.

Patient Profiles

According to a retrospective review of the surgical database in our institution between January 2001 and December 2010, we found a total of 160 patients who underwent staged single-ventricle palliation. Among them, 33 patients (20.6 % [male = 25, female = 8]) also underwent AVV repair or AVV replacement. The median age of patients with initial valve repair or replacement was 3.4 years (range 0.3–26.6). Heterotaxy syndrome ($n = 19$ [57.6 %]) was most frequently observed, followed by right ventricle–type [14] univentricular heart (UVH) ($n = 10$ [30.3 %]), left ventricle (LV)–type UVH ($n = 2$ [6.1 %]), and unbalanced AV septal defect (AVSD) ($n = 2$ [6.1 %]) (Table 1).

AV Valve Morphology and Surgical Technique

The most commonly observed morphological valve abnormality in our institute was annular dilatation of the AV valve ($n = 17$ [37.0 %]) followed by valve thickening ($n = 10$ [21.7 %]), prolapse ($n = 7$ [15.2 %]), and cleft ($n = 7$ [15.2 %]). The valve repair techniques used were the edge-to-edge technique ($n = 12$ [37.5 %]), cleft closure ($n = 7$ [21.9 %]), commissuroplasty ($n = 4$ [12.5 %]), annuloplasty ($n = 4$ [12.5 %]), and valvuloplasty ($n = 3$ [9.4 %]) (Fig. 1). A mechanical valve was implanted in all valve-replacement cases. The mean valve size was 29.5 ± 3.3 mm. The following valve types were used: Saint-Jude (St. Jude Medical, Minnesota [$n = 7$]), On-X (On-X Life Technologies, Austin, TX [$n = 3$]), and Carbomedics (CM; Carbomedics, Austin, TX [$n = 1$]).

Table 1 Preoperative patient profiles

Demographics	No. (%) or median (range) ($n = 33$)
Initial valve repair or replacement age (years)	3.4 (0.3–26.6)
Sex	
Male	25 (75.8)
Female	8 (24.2)
Diagnosis	
Heterotaxy syndrome	19 (57.6)
UVH (RV type)	10 (30.3)
UVH (LV type)	2 (6.1)
Unbalanced AVSD	2 (6.1)
Median follow-up duration (y)	6.0 (0.1–14.1)

AVSD atrioventricular septal defect, *LV* left ventricle, *RV* right ventricle, *UVH* univentricular heart

Clinical Outcome Assessment

The median follow-up duration was 6.0 years (range 0.1–14.1). The AVVR grading scale of 0–4 (0 = none, 1 = trivial, 2 = mild, 3 = moderate, and 4 = severe) was applied by four cardiologists in our institution. A successful outcome was defined as improving valve regurgitation to grade 0–2 after valve repair. Early repair was defined as repair before Fontan surgery. Because there is no relevant definition of ventricular dysfunction in single-ventricle physiology, we defined ventricular dysfunction as having more than two of the following three criteria: (1) gross morphologic ventricular dysfunction by echocardiography, (2) Tei index > 0.6, and (3) $dP/dt < 800$ mm Hg/s. Ventricle dysfunction in the early stage was defined as development before Fontan surgery. The primary end points were deterioration of the AVVR degree (valve durability) and freedom from mortality at latest follow-up.

Statistical Analysis

Data are expressed as mean ± SD or median including range. Survival was estimated by the Kaplan–Meier method and defined as the time elapsed from the valve repair or replacement date to death or latest known follow-up date. Log-rank test was used for comparisons between factors. Analyses were performed using Fisher's exact test for categorical variables. Statistical analyses were performed using SPSS 19.0 software for Windows (SPSS, Chicago, IL), and $p < 0.05$ was considered statistically significant.

Results

Indication and Timing of AVV Repair or Replacement

More than moderate degree of AVVR in echocardiography was our indication for adding AVV repair or replacement to a planned staged single-ventricle palliation. If the valve morphology was difficult to repair or if ventricle dysfunction was detected, we preferred valve replacement. Twenty-seven valve repairs (2 of 33 [81.8 %]) and 6 valve replacements (6 of 33 [18.2 %]) were performed at the

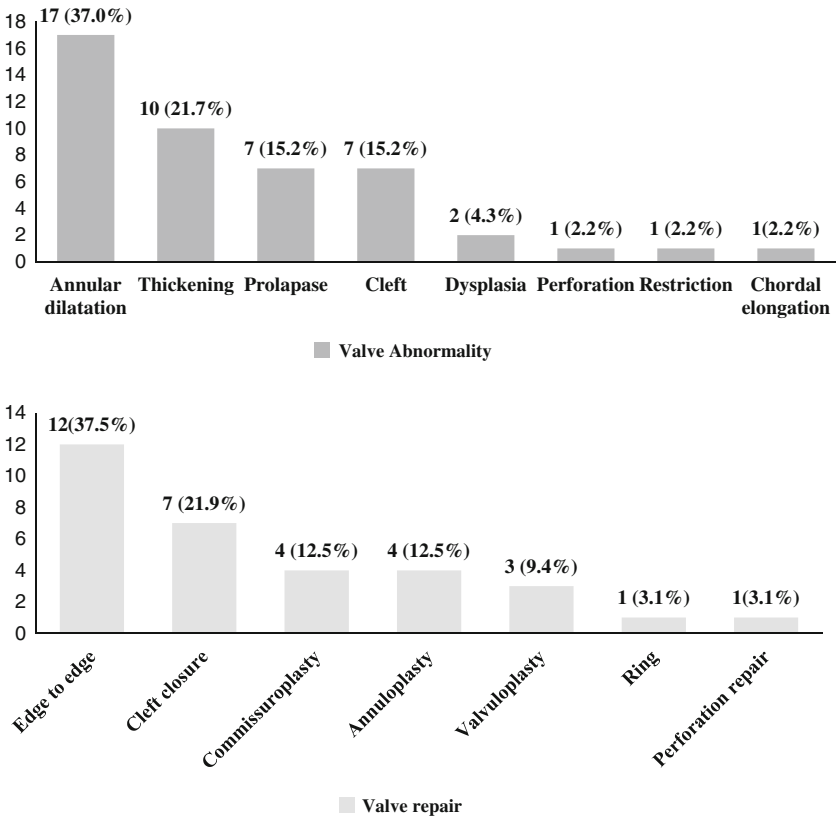

Fig. 1 AV valve morphology and valve repair surgical technique. Annular dilatation was the most commonly observed valve abnormality, and the edge-to-edge technique was the most commonly used surgical technique

initial surgery. Among the 11 patients requiring redo valve surgery due to progressed valve regurgitation, these were performed for valve repair in 6 patients (6 of 11 [54.6 %]) and for valve replacement in 5 patients (5 of 11 [45.9 %]). First-time valve surgeries were performed in valve repairs with concurrent BCPS surgeries ($n = 11$ [33.3 %]), between the BCPS and Fontan surgeries ($n = 3$ [9.1 %]) (interstage), at Fontan surgery ($n = 7$ [21.2 %]), and after Fontan surgery ($n = 6$ [18.2 %]). All initial valve replacement surgeries were performed after Fontan ($n = 6$ [18.2 %]). Second-time valve repairs were performed during ($n = 4$ [36.4 %]) and after Fontan surgery ($n = 2$ [18.2 %]). Second-time valve replacements were performed during the period between the BCPS and Fontan surgeries ($n = 1$ [9.1 %]), during Fontan surgery ($n = 2$ [18.2 %]), and after Fontan surgery ($n = 2$ [18.2 %]) (Table 2).

Analysis According to Valve and Ventricle Type

The diagnoses were divided into two groups: nonheterotaxy syndrome and heterotaxy syndrome (right isomerism and left isomerism). Common AV valve type and tricuspid valve dominant type showed similar incidence in the nonheterotaxy group (4 of 12 [33.3 %] vs. 5 of 12 [41.7 %], respectively) and left isomerism group in the heterotaxy group (2 of 5 [40.0 %] vs. 2 of 5 [40.0 %], respectively). However, the common AV valve type was dominant in the right isomerism subgroup of the heterotaxy group (14 of 16 [87.5 %]). Almost all patients (25 of 33 [75.8 %]) showed an RV-type ventricle in both the nonheterotaxy and heterotaxy groups (Fig. 2).

Table 2 Timing of AVV repair or replacement

Times	Group	Valve repair (%)	Valve replacement (%)
Initial surgery	Nonheterotaxy	9 (27.3)	0 (0)
	Heterotaxy	18 (54.5)	6 (18.2)
Redo surgery	Nonheterotaxy	2 (18.2)	1 (9.1)
	Heterotaxy	4 (36.4)	4 (36.4)
Initial valve surgery			
Stage II		11 (33.3)	0 (0)
Interstage		3 (9.1)	0 (0)
Fontan		7 (21.2)	0 (0)
After Fontan		6 (18.2)	6 (18.2)
Second valve surgery			
Stage II		0 (0)	0 (0)
Interstage		0 (0)	1 (9.1)
Fontan		4 (36.4)	2 (18.2)
After Fontan		2 (18.2)	2 (18.2)

AVV atrioventricular valve

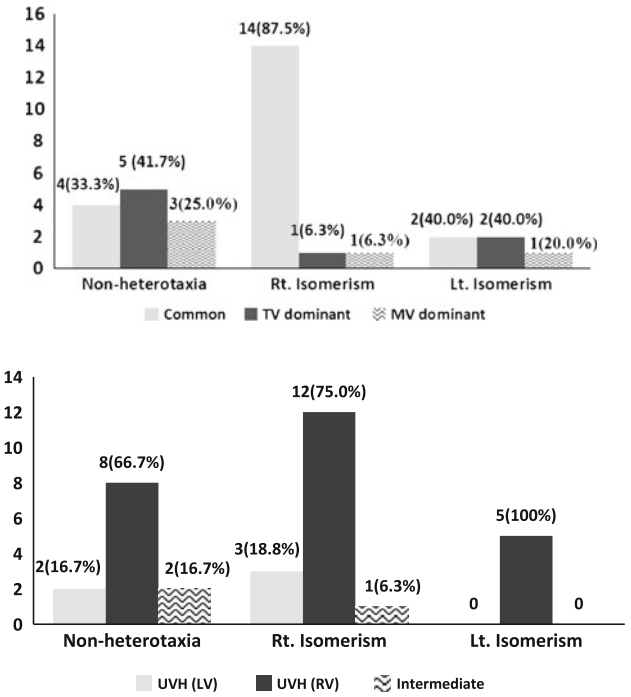

Fig. 2 Analysis according to valve and ventricle types. *Lt* left, *MV* mitral valve, *Rt* right, *RV* right ventricle, *TV* tricuspid valve

Mortality and Morbidity

Patients with valve repair or replacement experienced no early mortality; however, six patients had late mortality ($n = 5$ in the valve repair group and $n = 1$ in the valve replacement group). Four mortalities occurred in the right isomerism subgroup of the heterotaxy group, and two mortalities occurred in the unbalanced AVSD group. In the heterotaxy group, two patients who had ventricle dysfunction with severe valve regurgitation in the first palliation period died due to low cardiac output between the BCPS and Fontan surgeries (4.9 and 1.8 months after valve surgery, respectively). Two other patients died after surgery, one from infective endocarditis (2.7 months after valve repair) and one from postoperative cerebral infarct (2.05 years after valve repair). In the unbalanced AVSD group, one patient died from pneumonia at the age of 8 years (5.58 years after valve repair). Another patient died from poor ventricle function and respiratory failure at the age of 23 and had an underlying condition of protein-losing enteropathy and subsequent Fontan conversion (35 days after valve repair).

There were seven morbidities: arrhythmia ($n = 2$), paravalvular leakage ($n = 1$), postoperative bleeding ($n = 1$), postoperative intracerebral hemorrhage ($n = 1$), mediastinitis ($n = 1$), and chylothorax ($n = 1$). There was no morbidity related to anticoagulation in the valve replacement group. There were two redo surgeries in the valve replacement group. One young patient received the valve replacement because of a mechanical valve stenoinsufficiency due to growth. Another patient had postoperative paravalvular leakage after valve replacement. This patient subsequently underwent paravalvular leakage repair on postoperative day 3.

Survival Analysis and Freedom from Reoperation

Freedom from mortality in the valve replacement group was higher than that for patients in the valve repair group, although this did not reach statistical significance (90.9 ± 8.7 vs. 68.8 ± 12.2 % at 7 years, respectively, $p = 0.28$). Regarding factors affecting survival, Blalock–Taussig (BT) shunt as first palliation ($p = 0.04$) and arrhythmia ($p = 0.01$) were significantly associated with mortality according to log-rank test. However, heterotaxy ($p = 0.88$), common valve type ($p = 0.07$), ventricle type ($p = 0.55$), right isomerism ($p = 0.23$), and requiring valve surgery before Fontan surgery ($p = 0.30$) were not associated with mortality according to log-rank test (Fig. 3).

Freedom from reoperation in the valve replacement group was significantly higher than that in the valve repair group (67.0 ± 9.7 and 44.6 ± 11.2 % at 5 and 6 years, respectively, $p = 0.03$). Cases requiring valve repair or replacement before Fontan surgery ($p = 0.02$), having a mitral or tricuspid dominant AV valve ($p = 0.005$), and being of male sex ($p = 0.04$) were significantly associated with valve durability (Fig. 4). However, heterotaxy ($p = 0.88$), BT shunt ($p = 0.17$) or pulmonary artery banding ($p = 0.22$) as first palliation, isomerism type ($p = 0.23$), and ventricular dysfunction ($p = 0.35$) were not significantly associated with valve durability. An analysis stratified by ventricular dysfunctions showed that cases requiring valve repair or replacement before Fontan surgery ($p = 0.017$) were a risk factor for valve durability (Fig. 5).

Four patients with ventricular dysfunction in the early stage underwent valve repair or replacement. Among them, three patients (3 of 4 [75 %]) continued to experience poor ventricular function at the latest follow-up echocardiography. However, seven patients with ventricular dysfunction developing in the late stage underwent valve repair or replacement. Among them, five patients (5 of 7 [71.4 %]) had improved at the latest follow-up echocardiography (Fig. 6).

Discussion

In this study, we investigated the risk factors of valve durability after valve repair as well as the factors impacting survival. We also identified that early aggressive valve

repair or replacement, which is our surgical policy if it is needed, was important for establishment of successful Fontan circulation. The incidence of valve regurgitation at the latest follow-up and mortality were not high compared with other centers [1, 9, 17].

There is still controversy over the optimal timing of AV valve surgery. Honjo et al. [9] reported that the major causes of AVVR were valvar or subvalvar morphological abnormalities [16] rather than volume overloading or ventricle dysfunction. These investigators insisted that volume overloading, especially after shunt palliation, was not decreased after a bidirectional cavopulmonary connection [6]; thus, they recommended early period repair to decrease the risk factors for cavopulmonary circulation. Kwak et al. [13] reported that earlier AV valve operations for AV valve regurgitation tended to have better AV valve function at the mid-term period. In contrast, Mahle et al. [15] reported that AVVR improves in some patients after bidirectional cavopulmonary connection due to decreased volume loading [3]; thus, valvuloplasty is not justified in all patients with moderate preoperative AVVR. Hancock et al. [7] also reported that if there is a mild degree of valve regurgitation before a bilateral cavopulmonary connection, valve regurgitation improvement can be expected due to the volume decrease after the bilateral cavopulmonary connection. These conflicting results make it difficult to decide on the surgical treatment plan.

Some reports have mentioned that AVVR can be neutralized by valve repair alone [2, 17]. Patients who require valve repair in the early stage, who have a common AV

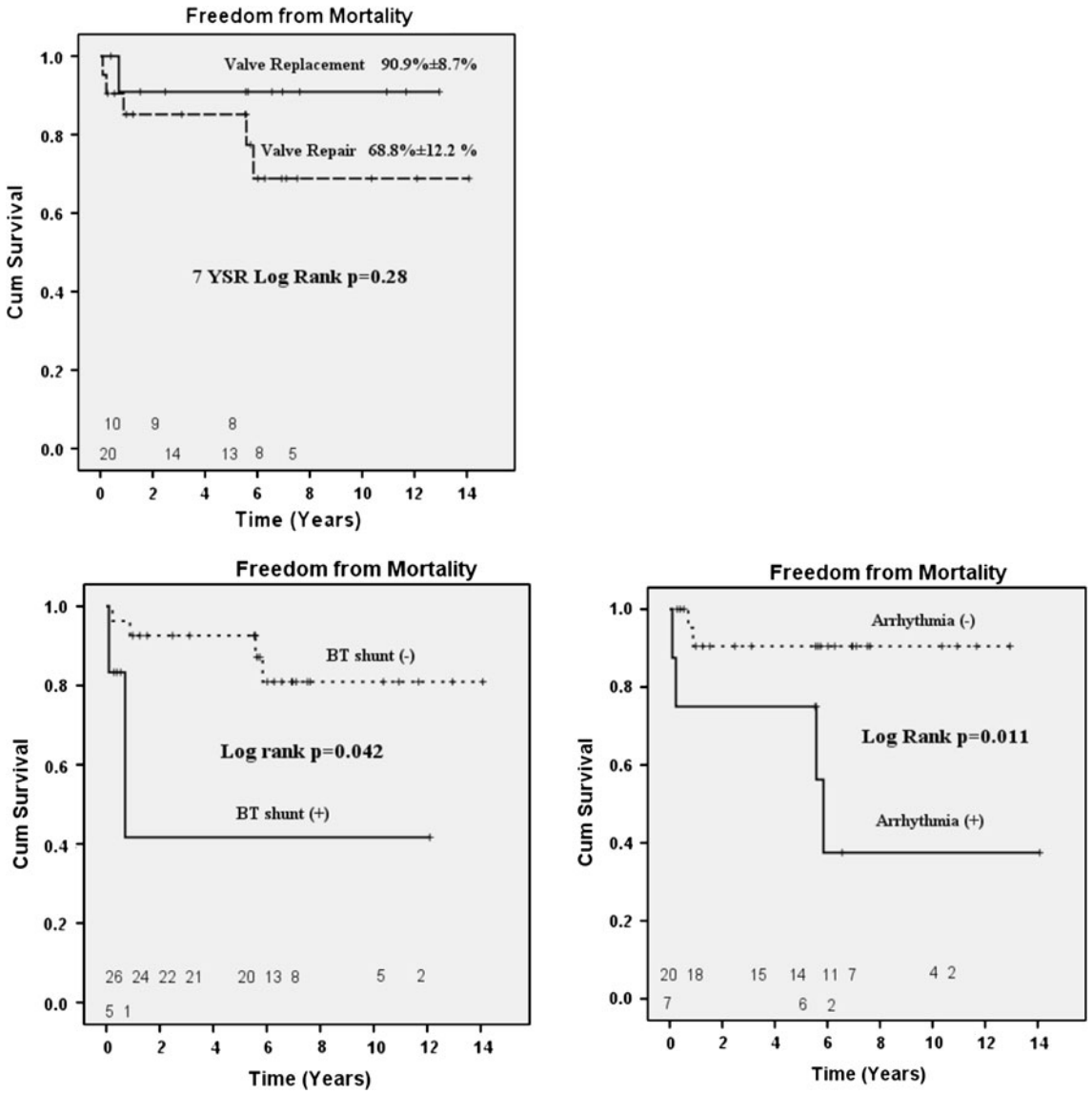

Fig. 3 Freedom from mortality and risk factors affecting survival. *BT* Blalock-Taussig, *Cum* cumulative, *YSR* year survival rate

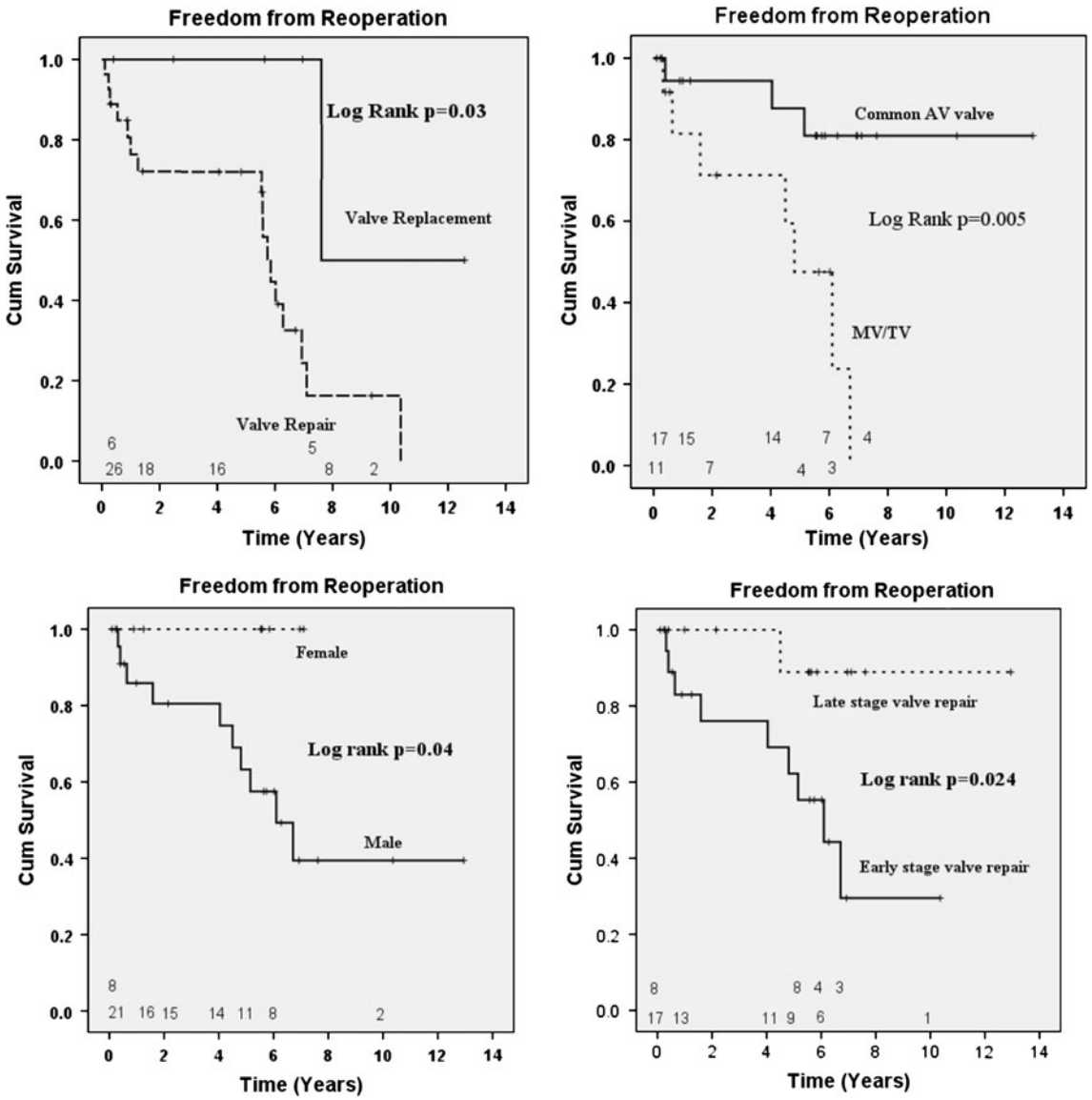

Fig. 4 Freedom from reoperation and risk factors for valve durability. *AV* atrioventricular, *Cum* cumulative, *MV* mitral valve, *TV* tricuspid valve

valve, and who are of male sex showed valve regurgitation progression in this study. These factors could not guarantee valve durability through valve repair alone.

Seventy-five percent of patients who had early ventricular dysfunction with valve regurgitation in this study did not show improved ventricular dysfunction, even if the valve repair was successful at the latest follow-up echocardiography. In contrast, 71.4 % of the patients developing ventricular dysfunction in the late stage showed restored ventricular function at the latest follow-up echocardiography. This ventricular dysfunction with valve regurgitation affected survival in this study. Thus, we speculated that early aggressive valve surgery was mandatory. The results of the AV valve replacement in this study were acceptable regarding survival and morbidity compared with other studies [14]. Thus, AV valve replacement may be one surgical option in these cases.

Heterotaxy syndrome is associated with several risk factors: arrhythmia, total anomalous pulmonary venous connection, and common AV valve [11, 12]. The right isomerism subgroup in the heterotaxy group especially did not show a good outcome [5, 8]. Kim et al. [12] reported that AVVR grade gradually increased even after Fontan surgery at the latest follow-up in the heterotaxy group. Thus, heterotaxy syndrome is still challenging to manage. Twenty-one (21 of 33 [63.6 %]) patients had heterotaxy syndrome in this study; 16 (16 of 21 [76.2 %]) patients had a common AV valve; and 17 (17 of 21 [81.0 %]) patients were right ventricle dominant. A common AV valve and RV-type single ventricle have been known to be important

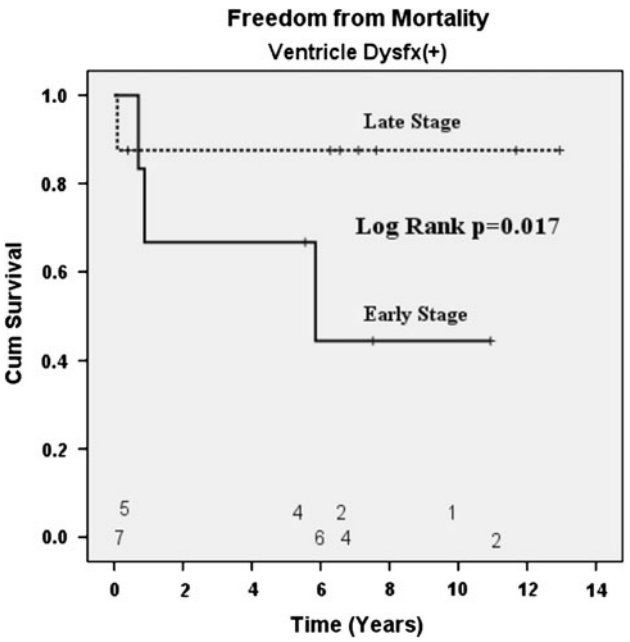

Fig. 5 Freedom from mortality according to valve repair with ventricle dysfunction patients. *Cum* cumulative, *Dysfx* dysfunction

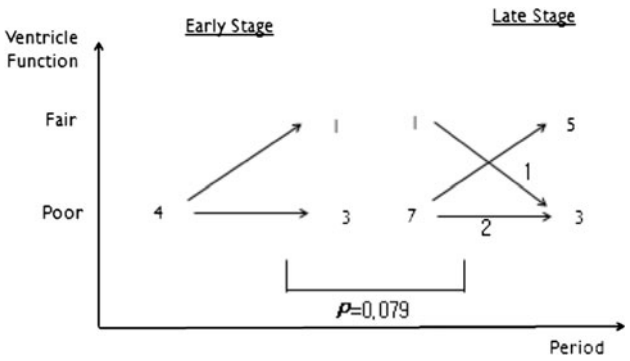

Fig. 6 Ventricle dysfunction at latest follow-up echocardiography according to period of development. Patients who had poor ventricle function in the early stage with valve regurgitation tended to have ventricular dysfunction at latest follow-up, even after valve repair

risk factors for patients with Fontan circulation [4, 18], and these risk factors do not guarantee valve durability even if the valve repairs were successful. However, heterotaxy syndrome was not a risk factor for valve durability and mortality in this study. We speculated that early aggressive valve repair might maintain valve durability and survival. Aggressive valve surgery, including valve replacement in the heterotaxy group, was performed. Four cases of AV valve replacement among the eight redo surgeries (50 %) were performed in the heterotaxy group. Only one case of mortality associated with valve replacement was observed in the valve-replacement group. If the valve morphology was difficult to repair or if ventricle dysfunction was detected, temerarious valve repair may have aggravated valve regurgitation and ventricular dysfunction. We preferred valve replacement in the above-mentioned cases.

Limitations

Despite the large number of patients with single-ventricle physiology, the number of patients with more than moderate-degree AVVR was relatively small. This may have limited the risk factor analysis of mortality and valve durability. In addition, the retrospective design relied on various readers. There is also no definite indication of valve replacement; it was a surgeon's preference.

Conclusion

Ventricular dysfunction with AV valve regurgitation in the early stage affects valve durability and persistent ventricular dysfunction although it did not affect mortality. Thus, successful repair in the early stage before ventricular dysfunction develops may improve later outcomes. AV valve replacement may be one of the options for selected patients with poor valve morphology and ventricular dysfunction.

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