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Congenitally Corrected Transposition of the Great Arteries

Ventricular Function at the Time of Systemic Atrioventricular Valve Replacement Predicts Long-Term Ventricular Function

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Objectives The objective was to evaluate the systemic ventricular ejection fraction (SVEF) at the time of systemic atrioventricular valve (SAVV) replacement as a predictor of SVEF ≥1 year after surgery in patients with congenitally corrected transposition of the great arteries (CCTGA).

Background Progressive SAVV regurgitation causes systemic ventricular failure in CCTGA patients, who are commonly referred late for intervention. Survival after surgery is poor when the pre-operative SVEF is <44%.

Methods We retrospectively reviewed 46 patients (pre-operative SVEF ≥40% in 27 patients and <40% in 19 patients) with 2 good-sized ventricles, a morphologically right systemic ventricle, and SAVV regurgitation requiring surgery. Median follow-up was not different in patients with a pre-operative SVEF ≥40% (8.8 years) or <40% (7.7 years, $p = 0.36$).

Results Pre-operative SVEF was the only independent predictor of ≥1-year post-operative SVEF ($p < 0.0001$). The late SVEF was preserved (defined as ≥40%) in 63% of patients who underwent surgery with an SVEF ≥40% compared with 10.5% of patients who underwent surgery with an SVEF <40%. Pre-operative variables associated with late mortality were an SVEF ≤40%, a subpulmonary ventricular systolic pressure ≥50 mm Hg, atrial fibrillation, and New York Heart Association functional class III to IV.

Conclusions Post-operative systemic ventricular function after SAVV replacement can be predicted from the pre-operative SVEF. For best results, operation should be considered at an earlier stage, before the SVEF falls below 40% and the subpulmonary ventricular systolic pressure rises above 50 mm Hg. (J Am Coll Cardiol 2011;57:2008–17) © 2011 by the American College of Cardiology Foundation

In congenitally corrected transposition of the great arteries (CCTGA), atrioventricular and ventriculoarterial discordance maintains the appropriate direction of blood flow. The morphological right ventricle (RV) supports the systemic circulation and the morphological tricuspid valve is the systemic atrioventricular valve (SAVV) (1). In up to 70% of cases, the SAVV is abnormal and may be inferiorly displaced: the so-called Ebstein's anomaly of the SAVV (2,3). It is the presence of an anatomically abnormal SAVV rather than ventricular dilatation and dysfunction that predicts the occurrence of regurgitation (3). SAVV regurgitation may also occur after closure of a ventricular septal defect (4). In the series of Prieto et al. (3), SAVV regurgitation was the only independent predictor of death in CCTGA. In a retrospective cohort, more than 50% of deceased patients had systemic ventricular failure, associated with severe SAVV regurgitation in most cases (5).

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Beauchesne et al. (6) found that 53% of adult CCTGA patients are referred late, already suffering from moderate to severe SAVV regurgitation and ventricular dysfunction for more than 6 months. In patients referred for SAVV replacement, 10-year post-operative survival is only 19.5% when the pre-operative systemic ventricular ejection fraction (SVEF) is below 44% (7). Survival with CCTGA thus

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appears closely linked to the presence of SAVV regurgitation and systemic ventricular dysfunction. Although it is often assumed that when the morphological RV functions as a systemic ventricle it is doomed to fail, failure most commonly occurs as a result of volume overload from SAVV regurgitation (3). If this holds true, then timely SAVV replacement may preserve ventricular function and, ultimately, improve long-term outcomes (3,7,8). This has been shown for the analogous situation of mitral regurgitation and left ventricular ejection fraction (9). The objectives of this study were: 1) to evaluate the SVEF at the time of SAVV replacement as a predictor of systemic ventricular function ≥1 year after surgery; and 2) to identify pre-operative variables that are associated with post-operative survival. The hypothesis is that patients with CCTGA undergoing SAVV replacement with a preserved SVEF (≥40%) maintain a preserved SVEF in the long term.

Methods

Patients. Patients with CCTGA were identified from the Mayo Clinic clinical databases. Inclusion criteria were: 1) SAVV regurgitation that required valve replacement performed at Mayo Clinic; and 2) a known SVEF at the time of SAVV replacement. Patients with pulmonary atresia or double outlet RV or who had a Fontan or a double-switch operation were excluded. Patients were grouped according to their SVEF (<40% or ≥40%). The patient selection is outlined in Figure 1. Follow-up was deemed complete if an SVEF was measured ≥1 year after surgery. The 12 patients who were without SVEF follow-up were included in the survival analysis.

After a review of records, 41% of patients with a pre-operative SVEF ≥40% had not returned for follow-up after year 2006 and were not known to be deceased, compared with only 11% of patients with a pre-operative SVEF <40%. It was possible that patients with a better systemic ventricular function were doing well and did not perceive the need to follow up in a tertiary care center such as ours. To strengthen this follow-up, 11 patients with a pre-operative SVEF ≥40% and no follow-up after year 2006 were surveyed with mailed questionnaires and brief phone interviews. Questionnaires were returned by 8 patients, 1 patient was reached by phone, and 2 patients could not be retraced. The protocol was approved by the Mayo Clinic Institutional Review Board.

Data collection. Medical records were retrospectively reviewed. A medication was deemed used if taken after surgical dismissal. Functional status was assessed with the Warnes-Somerville ability index (10), the New York Heart Association (NYHA) functional class, and the functional aerobic capacity. The primary outcomes examined were the SVEF and survival or freedom from heart transplantation ≥1 year after surgery.

Measurement of SVEF. SVEF measurements were extracted from reports of echocardiography, angiography, MRI, or CT angiograms performed preferentially at Mayo Clinic. Selected studies were reviewed by 2 investigators (F.P.M. and C.A.W.) when information was deemed insufficient or not available otherwise.

Assessment of SVEF by echocardiography is most frequently used at our institution, either by visual estimate (11) or additional M-mode and 2-dimensional measurements. Priority was given to MRI-derived SVEF, followed by echocardiography and angiography. An SVEF ≥40% was selected to define preserved systemic ventricular function on the basis of previous series (7,12).

The pre-operative SVEF measurement closest to surgery was recorded. The immediate post-operative SVEF was measured within 30 days of surgery or during the surgical hospitalization, whichever was longer. The late SVEF was the most recent measurement, obtained ≥1 year after surgery.

Hemodynamic and anatomic assessments. Data were preferentially abstracted from echocardiograms acquired with standardized protocols (13,14). A few patients only had angiograms, MRI, or CT angiograms. The SAVV regurgitation was assessed qualitatively as absent, trivial, mild, moderate, moderate to severe, and severe. Nonsystemic (or subpulmonary) atrioventricular valve regurgitant jet systolic velocity by continuous-wave Doppler was used for noninvasive estimation of the subpulmonary ventricular systolic pressure (SPVSP) (15). Ebstein's anomaly, prolapse, or dysplastic features defined an abnormal SAVV and were confirmed at surgical inspection.

SAVV replacement. Standard techniques for cardiopulmonary bypass were used. Cold potassium, blood cardioplegic solution has been used for myocardial protection since 1977. Given the poor late results of valvuloplasty, our institution has favored valve replacement in CCTGA patients (7). The benefits of this approach have also been reported by others (16).

Statistical analysis. Descriptive statistics for categorical variables are reported as frequency and percentage, whereas continuous variables are reported as mean ± SD or median (range) as appropriate. Categorical variables were compared between patients with pre-operative SVEF ≥40% and SVEF <40% using chi-square test or Fisher exact test where appropriate, and continuous variables were compared using 2-sample t test or Wilcoxon rank sum test where appropriate. Linear regression models were used to find univariate and multivariate predictors of late SVEF.

Abbreviations and Acronyms

CCTGA = congenitally corrected transposition of the great arteries

CT = computed tomography

FAC = functional aerobic capacity

MRI = magnetic resonance imaging

NYHA = New York Heart Association

PVOTO = pulmonary ventricular outflow tract obstruction

RV = right ventricle

SAVV = systemic atrioventricular valve

SPVSP = subpulmonary ventricular systolic pressure

SVEF = systemic ventricular ejection fraction

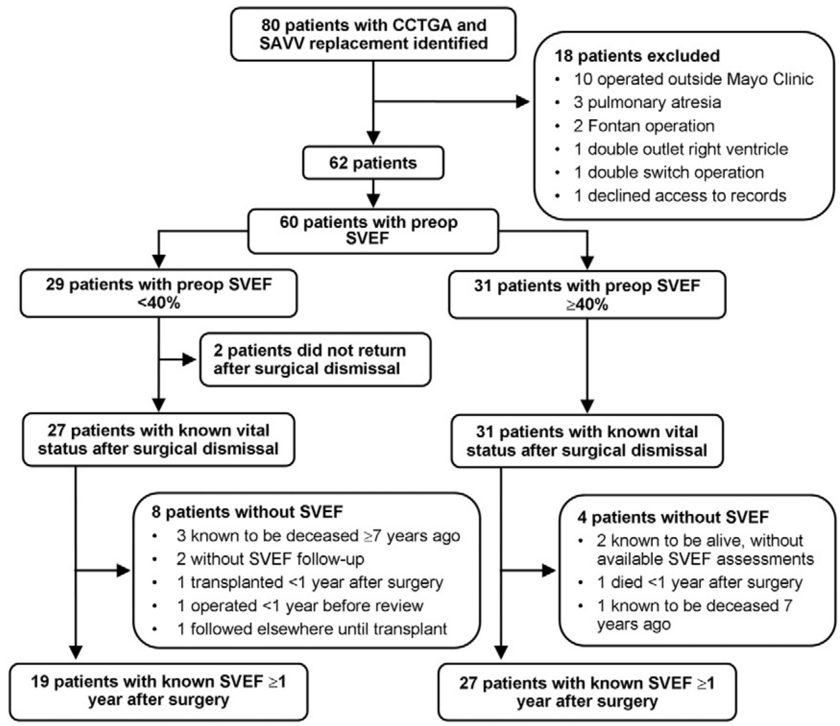

Figure 1 **Flow Chart of Patient Selection**

Two study groups were established on the basis of a pre-operative SVEF ≥ or <40%. All patients (n = 58) with a known vital status after surgical dismissal were included in the survival analysis. CCTGA = congenitally corrected transposition of the great arteries; preop = pre-operative; SAVV = systemic atrioventricular valve; SVEF = systemic ventricular ejection fraction.

The multivariable model considered univariately significant variables ($p < 0.05$) with model selection using the stepwise method (backward and forward methods resulted in the same model). All statistical tests were 2-sided with the alpha level set at 0.05 for statistical significance. The Kaplan-Meier method was used to estimate survival statistics. Cox regression models were used to find the risk factors for late mortality. When analyzing survival, the optimal cutoff point for the predictor pre-operative SVEF minimized the log-rank test p values (17). When analyzing predictors of late SVEF, we dichotomized preoperative SVEF at 35%, 40%, 45%, and 50% and used the dichotomized SVEF 1 by 1 to identify which variable best fits the linear regression model. Cutoff points should produce 2 groups with reasonable sample sizes.

Results

Pre-operative and operative characteristics. There were 46 patients, 5 to 72 years of age with a mean age of 40.8 ± 14.8 years. Twenty-seven patients had a pre-operative SVEF >40%, and 19 patients had a pre-operative SVEF <40% (Fig. 1). The pre-operative SVEF was evaluated by echocardiography (n = 43, 93%), by angiography (n = 2), and by MRI (n = 1). The groups' pre-operative characteristics are outlined in Table 1. Patients who underwent surgery with an SVEF ≥40% were younger. Males and smokers were more common among patients with a pre-operative SVEF <40%. The functional aerobic capacity, when available, was better in patients with a preserved pre-operative SVEF. No patient was in NYHA functional class IV heart failure. Heart failure medications were commonly used, regardless of ventricular function. The SAVV was abnormal and the mean SPVSP moderately elevated in most patients. Prior operations were performed in 5 patients (26.3%) with a pre-operative SVEF <40% and in 4 patients (14.8%) with a pre-operative SVEF ≥45%. The most common operation was ventricular septal defect closure (6 of 46 patients) followed by resection of a subpulmonary membrane and pulmonary atrioventricular valve repair (2 of 46 patients each).

Operative characteristics are presented in Table 2. All patients underwent SAVV replacement, reflecting our institution's preference. The first operation was performed in 1979. All ball-in-cage prostheses were implanted before 1995. There is no correlation between the pre-operative SVEF and the operative year ($r = 0.173$, $p = 0.1953$). One patient had a previous attempt at SAVV repair. Chordal preservation was most often performed in patients with a pre-operative SVEF <40%, likely reflecting a concern to

Table 1 Pre-Operative Characteristics

	n*	SVEF ≥40%	n*	SVEF <40%	p Value
Age at surgery (yrs)	27	39 ± 16 (5–72)	19	43 ± 13 (21–63)	0.42
Female	27	19 (70%)	19	4 (21%)	<0.001
SVEF (%)	27	46.2 ± 5.4	19	32.2 ± 4.9	<0.001
Time between SVEF measurement and surgery (days)	27	16 (1–456)	18	34 (1–120)	0.38
SAVV regurgitation grade	19		27		0.43
Moderate		2 (7%)		3 (16%)	
Moderate to severe		8 (30%)		3 (16%)	
Severe		17 (63%)		13 (68%)	
Abnormal SAVV	26	22 (85%)	18	15 (83%)	0.91
Ebstein-like anomaly	26	15 (58%)	18	9 (50%)	0.61
Subpulmonary ventricular systolic pressure (mm Hg)	24	49.0 ± 22.0	15	59.7 ± 31.8	0.20
Mean cardiothoracic ratio	12	0.52 ± 0.09	7	0.56 ± 0.10	0.39
Associated anomalies	27		19		
Pulmonary outflow obstruction		9 (33%)		9 (47%)	0.34
Ventricular septal defect		7 (26%)		6 (32%)	0.68
Atrial septal defect		10 (37%)		7 (37%)	0.99
High-grade atrioventricular block		9 (33%)		9 (47%)	0.34
Permanent pacemaker	27	5 (19%)	19	7 (37%)	0.16
Coronary artery disease	27	1 (4%)	18	3 (17%)	0.13
Diabetes mellitus	27	0 (0%)	19	0 (0%)	
Hypertension	27	1 (4%)	19	2 (11%)	0.36
Current or past smoker	27	6 (22%)	19	12 (64%)	0.03
Hypercholesterolemia	27	3 (11%)	19	3 (16%)	0.64
Warnes-Somerville ability index	26		19		0.35
1		14 (54%)		14 (74%)	
2		8 (31%)		4 (21%)	
3		4 (15%)		1 (5%)	
New York Heart Association functional class	26		19		0.68
I		12 (46%)		11 (58%)	
II		13 (50%)		7 (37%)	
III		1 (4%)		1 (5%)	
FAC† (%)	11	85.9 ± 14.5	13	62.6 ± 18.0	0.002
Pre-operative atrial fibrillation	27	7 (26%)	19	7 (37%)	0.43
Medication	27		19		
Angiotensin-converting enzyme inhibitor		19 (70%)		12 (63%)	0.61
Angiotensin receptor blocker		3 (11%)		1 (5%)	0.49
Beta-blocker		5 (19%)		3 (16%)	0.81
Loop diuretic		11 (41%)		8 (42%)	0.93
Spironolactone		1 (4%)		0 (0%)	0.40
Digoxin		9 (33%)		15 (79%)	0.003

Data are mean ± SD (range), n (%), mean ± SD, or median (range). $p < 0.05$ denotes a statistically significant difference between groups. *Number of patients with available data. †Using a Bruce treadmill protocol or a cardiopulmonary exercise test, the functional aerobic capacity is expressed as a percentage of expected when compared with the predicted value for sex and age.

FAC = functional aerobic capacity; SAVV = systemic atrioventricular valve; SVEF = systemic ventricular ejection fraction.

maintain ventricular geometry in these patients. One patient had a Maze procedure.

Post-operative outcomes. Post-operative outcomes are outlined in Table 3. Follow-up that included a late SVEF measurement was available at least until year 2005 for all but 1 patient, who was followed until year 2002. The median follow-up was not different between the groups (Table 3). There was no early mortality. Post-operative morbidity included a similar occurrence of atrial arrhythmias and reoperation in both groups. Reoperations included, in patients with a pre-operative SVEF ≥40%, 4 repeat SAVV replacements, 4 defibrillator implantations (3 for secondary prevention and 1 for primary prevention), 1 pulmonary atrioventricular valve replacement, 1 pericardial window, 1 delayed sternal closure, 1 re-exploration for tamponade, and resection, debridement, and homograft patch repair of a mycotic pseudoaneurysm of the ascending aorta in 1 patient. In patients with a pre-operative SVEF <40%, reoperations and re-interventions included 5 defibrillator implantations (4 for secondary and 1 for primary prevention, 1 biventricular pacemaker), 2 early re-explorations for bleeding, 2 pulmonary valve replacements, and 1 pulmonary atrioventricular valve replacement. The use of heart failure medications was more common than pre-operatively, regardless of ventricular function. The incidence of ventricular arrhythmias

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Table 2 Operative Characteristics

	n*	SVEF ≥40%	n*	SVEF <40%	p Value
SAVV replacement	27	27 (100%)	19	19 (100%)	
Type of prosthetic valve	27		19		0.19
Ball-in-cage		4 (15%)		4 (21%)	
Tilting disc		16 (59%)		14 (74%)	
Bioprosthesis		7 (26%)		1 (5%)	
Previous SAVV replacement	27	0 (0%)	19	0 (0%)	
Previous SAVV repair	27	1 (4%)	19	0 (0%)	0.40
Bypass time (min)	26	123 ± 53	19	128 ± 42	0.72
Chordal preservation	27	3 (11%)	19	8 (42%)	0.0322
Concomitant procedures	27	15 (56%)	19	12 (63%)	0.37
Atrial septal defect closure		8 (30%)		5 (26%)	0.81
Ventricular septal defect closure		4 (15%)		2 (11%)	0.67
Pulmonary outflow surgery		1 (4%)		2 (11%)	0.95
Aortic valve replacement		1 (4%)		2 (11%)	0.36

Data are n (%) or mean ± SD. $p < 0.05$ denotes a statistically significant difference between groups. *Number of patients with available data. Abbreviations as in Table 1.

and of pacemaker and defibrillator implantation was similar in both groups.

Prediction of post-operative SVEF. The SVEF ≥1 year after surgery was measured by echocardiography in 45 patients (98%) and by CT angiography in 1 patient. Early and late post-operative SVEF reflected pre-operative SVEF. The majority of patients (17 of 27 patients, 89.5%) who underwent surgery with a pre-operative SVEF ≥40% maintained an SVEF ≥40% at late follow-up (Fig. 2). The mean duration of cardiopulmonary bypass was significantly

Table 3 Post-Operative Outcomes

	n*	SVEF ≥40%	n*	SVEF <40%	p Value
Follow-up (yrs)	27		19		
Vital status		8.8 (1.7–24.2)		7.7 (1.7–18.2)	0.36
SVEF		7.6 (1.7–24.2)		5.4 (1.0–18.2)	0.15
Late mortality or cardiac transplantation	27	4 (15%)	19	7 (37%)	0.08
Late SVEF (%)	27	26.0 ± 10.5	19	37.4 ± 11.4	0.001
Early mortality	27	0 (0%)	19	0 (0%)	
Immediate post-operative SVEF (%)	24	40.1 ± 5.7	16	31.9 ± 8.6	0.003
Moderate or more residual SAVV regurgitation	25	2 (8%)	18	0 (0%)	0.31
Ventricular arrhythmias	27	7 (26%)	19	10 (52%)	0.06
Sudden death, ventricular fibrillation, or sustained VT		4 (15%)		6 (21%)	
Nonsustained VT or symptomatic PVCs		3 (11%)		8 (28%)	
New-onset atrial arrhythmias	27	14 (52%)	19	10 (53%)	0.95
Atrial fibrillation		5 (19%)		6 (32%)	
Atrial flutter		4 (15%)		3 (16%)	
Supraventricular tachycardia		3 (11%)		1 (5%)	
Permanent pacing	27		19		
Immediate post-operative		8 (30%)		4 (21%)	0.51
Late	27	3 (11%)	19	7 (37%)	0.0672
Admission for heart failure	27	7 (26%)	19	8 (42%)	0.25
Warnes-Somerville ability index 1 to 2	27	25 (93%)	19	17 (89%)	0.27
FAC (%)	16	81 ± 26	14	62 ± 10	0.0192
Reoperation	27	11 (41%)	19	11 (58%)	0.37
Medication	27		19		
Angiotensin-converting enzyme inhibitor		23 (85%)		16 (84%)	0.93
Angiotensin receptor blocker		7 (26%)		4 (21%)	0.70
Beta-blocker		15 (56%)		12 (63%)	0.61
Loop diuretic		15 (56%)		9 (47%)	0.58
Spironolactone		1 (4%)		5 (26%)	0.02
Digoxin		16 (59%)		15 (79%)	0.16

Data are median (range), n (%), or mean ± SD. $p < 0.05$ denotes a statistically significant difference between groups. *Number of patients with available data. PVC = premature ventricular contraction; VT = ventricular tachycardia; other abbreviations as in Table 1.

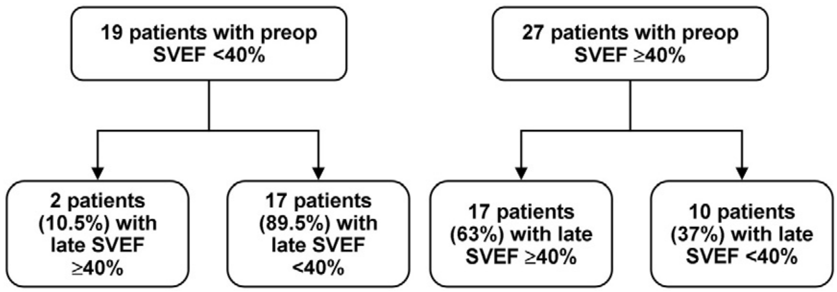

Figure 2 **Outcome of Post-Operative Ventricular Function According to Pre-Operative SVEF**

More patients with a preserved pre-operative SVEF have an SVEF ≥40% at late follow-up (≥1 year). Abbreviations as in Figure 1.

longer in the 10 patients whose SVEF decreased below 40% after surgery (158 ± 60 min vs. 101 ± 36 min in patients who kept a post-operative SVEF ≥40%, $p = 0.0058$). The pre-operative SVEF was the most significant predictor of the late post-operative SVEF by multivariate regression analysis (estimate 0.83; 0.49 to 1.16; $p < 0.0001$) (Table 4).

Table 4 **Univariate and Multivariate Analysis for Predictors of the Late Post-Operative SVEF**

	Estimate	95% Confidence Interval	p Value
Univariate analysis			
Complex CCTGA*	−5.53	−12.38 to 1.32	0.11
Age at surgery	−0.11	−0.35 to 0.13	0.38
Pre-operative SVEF	0.83	0.49 to 1.16	<0.001
Duration of follow-up	0.0006	−0.0014 to 0.0027	0.56
Paced rhythm	−6.42	−13.38 to 0.55	0.07
Abnormal SAVV	−5.03	−14.48 to 4.41	0.30
Known coronary artery disease	−7.1	−19.4 to 5.2	0.26
Hypertension	−2.03	−16.26 to 12.20	0.78
Tobacco use	−7.16	−14.15 to −0.17	0.045
Hypercholesterolemia	−3.62	−14.01 to 6.77	0.50
Warnes-Somerville ability index			
3	9.99	−1.07 to 21.06	0.08
2	−1.53	−9.40 to 6.33	0.70
New York Heart Association functional class			
III	4.63	−12.79 to 22.06	0.60
II	1.31	−5.91 to 8.53	0.72
Pre-operative atrial fibrillation	−2.00	−9.63 to 5.61	0.61
Pre-operative use of diuretics	−0.63	−7.69 to 6.43	0.86
Concomitant operation with SAVV replacement	−2.06	−9.20 to 5.09	0.573
Post-operative use of ACEI or ARB	0.24	−23.88 to 24.36	0.99
Post-operative use of beta-blockers	−0.052	−7.20 to 7.09	0.99
Post-operative use of spironolactone	−9.72	−19.78 to 0.34	0.06
Multivariate analysis			
Pre-operative SVEF	0.83	0.49 to 1.16	<0.0001

$p < 0.05$ denotes statistical significance. *Defined as an associated ventricular septal defect or pulmonary outflow obstruction.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; CCTGA = congenitally corrected transposition of the great arteries; other abbreviations as in Table 1.

After adjusting for it, none of the other variables tested were significant (Table 4).

Risk factors for late mortality. The late post-operative mortality or need for cardiac transplantation was 15% in patients with a pre-operative SVEF ≥40% and 37% in those with a pre-operative SVEF <40% ($p = 0.08$). Kaplan-Meier survival analysis included 58 patients with known vital status after surgical dismissal (Fig. 1). All but 3 of these patients had a known vital status until year 2005 or later; 2 patients were followed until year 2001 and 1 until year 2002. The estimates for 1-, 5-, and 10-year post-operative survival or freedom from transplantation were 96.5%, 90.6%, and 64.1%, respectively. Variables tested as risk factors for late mortality or transplantation are listed in Table 5. A higher pre-operative SVEF was associated with better outcomes (hazard ratio [HR]: 0.94; 95% confidence interval [CI]: 0.89 to 0.99; $p = 0.02$) (Table 5). Patients with a pre-operative SVEF ≥40% had a significantly better post-operative survival or freedom from transplantation ($p = 0.02$) (Fig. 3). A pre-operative SPVSP ≥50 mm Hg predicted post-operative mortality or transplantation (HR: 6.42; 95% CI: 1.44 to 28.53; $p = 0.02$) (Fig. 4). A high SPVSP may reflect either a pulmonary ventricular outflow tract obstruction (PVOTO) or pulmonary hypertension; 13 patients had both a pre-operative SPVSP ≥50 mm Hg and a history of PVOTO. Their 10-year post-operative survival was 41.2% compared with 71.4% in patients without these characteristics. A history of PVOTO alone did not substantially impair late survival (HR 0.98; 95% CI: 0.38 to 2.53; $p = 0.96$). Any pre-operative atrial fibrillation or NYHA functional class III to IV was also associated with post-operative mortality or transplantation (Table 5). The post-operative use of a beta-blocker (HR: 0.29; 95% CI: 0.11 to 0.77; $p = 0.01$) and a higher early post-operative SVEF (HR: 0.92; 95% CI: 0.85 to 0.98; $p = 0.02$) was associated with a substantially better long-term outcome (Table 5).

Identification of the best pre-operative SVEF threshold. We tested 4 pre-operative SVEF thresholds (35%, 40%, 45%, and 50%) to predict late SVEF and survival. When analyzing the pre-operative SVEF as a predictor of post-

Table 5 Univariate Cox Regression Model to Predict Post-Operative Mortality or Need for Cardiac Transplantation (n = 58)

	Hazard Ratio	95% Confidence Interval	p Value
Pre-operative SVEF	0.94	0.89–0.99	0.02
Complex CCTGA	0.77	0.30–1.97	0.59
Paced rhythm	2.15	0.75–6.13	0.15
Age at surgery	1.02	0.98–1.05	0.35
Abnormal SAVV	0.65	0.18–2.32	0.51
Previous surgical repair	0.95	0.27–3.30	0.88
Known coronary artery disease	4.13	0.88–19.31	0.07
Hypertension	1.44	0.19–10.94	0.72
Tobacco use	1.50	0.58–3.85	0.40
Hypercholesterolemia	0.64	0.08–4.92	0.67
Warnes-Somerville ability index 3 to 4	1.31	0.28–6.24	0.73
New York Heart Association functional class III to IV	6.37	1.17–34.58	0.03
Pre-operative atrial fibrillation	2.69	1.06–6.84	0.04
Pre-operative use of diuretics	1.50	0.59–3.82	0.40
Concomitant operation with SAVV replacement	1.39	0.49–3.93	0.53
Post-operative use of beta-blockers	0.29	0.11–0.77	0.01
Post-operative use of spironolactone	0.81	0.18–3.56	0.78
Pre-operative SPVSP	1.02	1.00–1.04	0.01
Pre-operative FAC	0.98	0.94–1.02	0.37

$p < 0.05$ denotes statistical significance. *Defined as an associated ventricular septal defect or pulmonary outflow obstruction.

CCTGA = complex congenitally corrected transposition of the great arteries; SPVSP = subpulmonary ventricular systolic pressure; other abbreviations as in Table 1.

operative survival, a cutoff SVEF of 40% produced the lowest log-rank test p value. When analyzing the pre-operative SVEF as a predictor of late SVEF, 40%, 45%, and 50% were not significantly different in predicting late SVEF. However, there were only 8 patients with pre-operative SVEF ≥50%.

Discussion

Summary of results. Our study included patients with CCTGA, 2 good-sized ventricles, a systemic RV, and SAVV regurgitation requiring valve replacement. Most patients were referred in adulthood. The pre-operative SVEF was the only determinant of long-term SVEF, which was mostly preserved if SAVV replacement was performed with an SVEF ≥40%. Pre-operative variables that predicted late mortality or cardiac transplantation include SVEF, SPVSP, NYHA functional class III to IV, and atrial fibrillation.

SAVV regurgitation and ventricular dysfunction. As patients with CCTGA age, their often abnormal SAVV (Table 1) becomes regurgitant (3). The systemic RV is intolerant to volume overload, and its performance eventually decreases (8,18,19). Valvular and ventricular dysfunctions then participate in a vicious cycle leading to further systemic ventricular dysfunction and failure (20). Other causes of failure of the systemic RV include mismatch in oxygen supply and demand, associated defects, prior intracardiac operations, arrhythmias, and pacemaker implantation (1,2,19). However, CCTGA patients can maintain good systemic ventricular function and survive beyond the 6th decade in the absence of hemodynamic lesions (21,22). One patient in our series who was 71 years old at the time of SAVV replacement and had a pre-operative SVEF of 42% still has an SVEF of 48% at age 86 years, some 15 years after initial operation. If the regurgitation is severe, timely valve replacement is indicated to prevent further RV failure.

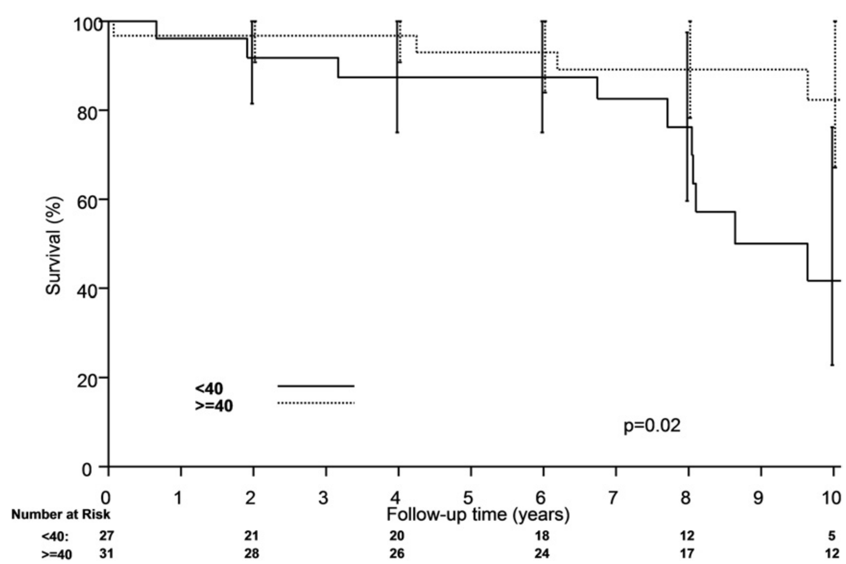

Figure 3 Survival After SAVV Replacement in CCTGA Patients According to Pre-Operative SVEF

More CCTGA patients who underwent surgery with an SVEF ≥40% remain free of death or cardiac transplantation at follow-up. Abbreviations as in Figure 1.

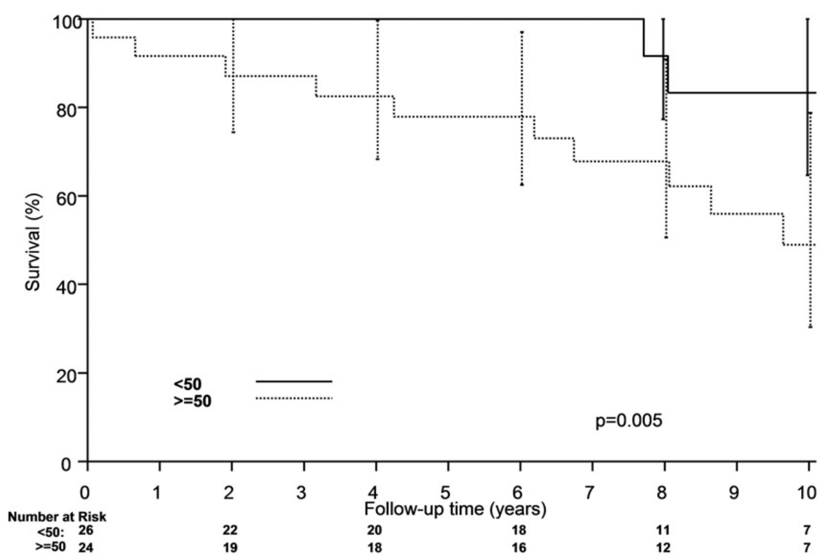

Figure 4 **Survival After SAVV Replacement in CCTGA Patients According to Pre-Operative SPVSP**

Fewer patients remain free of death or cardiac transplantation at follow-up with a pre-operative SPVSP ≥50 mm Hg (p = 0.012). PVOTO = pulmonary ventricular outflow tract obstruction; SPVSP = subpulmonary ventricular systolic pressure; other abbreviations as in Figure 1.

Predictors of late systemic ventricular function. Pre-operative SVEF was the only independent predictor of late ventricular function. SAVV replacement did not improve SVEF in patients with a pre-operative SVEF <40% (Fig. 2). A subset of patients with a pre-operative SVEF ≥40% developed ventricular dysfunction after SAVV replacement. The duration of cardiopulmonary bypass was substantially longer in these patients, which may have influenced ventricular function. It is also possible that SAVV replacement failed to halt an already established progressive ventricular dysfunction in these patients. The median pre-operative SVEF in these patients was 42% (range 40% to 48%). Operation at an even earlier stage may be required to truly preserve SVEF.

A paced rhythm did not predict late SVEF or post-operative mortality. Cardiac resynchronization therapy may improve the hemodynamics of the failing systemic RV (23,24), but is technically challenging (24,25).

Post-operative survival. In our study, the 10-year post-operative survival or freedom from cardiac transplantation was 64.1%. An SAVV replacement may be only moderately successful at improving survival because it was performed too late (6). In the series by van Son et al. (7) from our institution, all patients with pre-operative SVEF ≥44% were alive at 10 years follow-up. Our results suggest that, to improve survival, SAVV replacement should be performed with a pre-operative SVEF ≥40% (Fig. 3). Patients who underwent surgery with an SVEF ≥50% were underrepresented in the survival analysis (10 of 58 patients) and may have had an even better outcome.

Pre-operative atrial fibrillation, either paroxysmal or sustained, was associated with post-operative mortality or need for cardiac transplantation. Atrial fibrillation likely reflects more advanced sequelae of SAVV regurgitation on the atria. In the absence of other surgical indications, we propose that patients with atrial fibrillation be considered for earlier operation, which would include a Maze procedure.

We observed a very significant association between the pre-operative SPVSP and long-term mortality or need for transplantation. Consequently, outcomes may be improved if a high SPVSP is avoided before SAVV replacement. Patients with both PVOTO and high SPVSP have poorer outcomes and should be closely followed. A history of PVOTO alone did not influence the late survival or need for cardiac transplantation.

In a univariate analysis, the post-operative use of beta-blockers was associated with better survival or freedom from transplantation. Among 27 patients taking beta-blockers post-operatively, 63% had atrial arrhythmias and 40.7% had ventricular arrhythmias, compared with 26.3% and 31.6%, respectively, in patients not taking beta-blockers. Beta-blockers did not improve outcomes in a randomized trial that included pediatric patients with systemic right ventricular dysfunction (26) and must be used cautiously in CCTGA patients, as they may precipitate atrioventricular block.

We cannot comment on the outcome of SAVV repair because all our patients underwent SAVV replacement. SAVV repairs have had disappointing intermediate and late results (16).

Evaluation of systemic right ventricular function. Challenges exist with the evaluation of the systemic right ventricular performance and relate to the chosen modality and criteria. In this study, echocardiographic assessment of

SVEF was the most commonly used method. Echocardiography in patients with CCTGA can be challenging due to dextrocardia and the requirements for unusual imaging planes (1). A visual estimate of SVEF relies heavily on experience and may in fact reflect a qualitative appreciation. Currently used normal values for SVEF are derived from small studies using radionuclide ventriculography (12,21). Angiography has also been used (18). Experience has shown that echocardiography can underestimate SAVV regurgitation in this setting, and we recommend consideration of angiography when the ventricular function declines and the cardiac silhouette enlarges without explanation (6). MRI holds promise in the evaluation of the RV (27).

The criteria for ventricular dysfunction have also been questioned (20). We identified that in this cohort, an SVEF of 40% best predicts both survival and late systemic ventricular function. The justification for choosing the lower threshold is that relatively few CCTGA patients present with a normal SVEF (6). Therefore, an SVEF threshold that discriminates between patients with a mildly depressed to normal SVEF (≥40%) and a moderately or severely depressed SVEF (<40%) is more likely to be useful in clinical practice. Ejection fraction depends on pre-load and afterload and may overestimate ventricular function with SAVV regurgitation. Other potential criteria are the dP/dt (20), the index of myocardial performance (28), and the response of SVEF to exercise (12).

Timing of surgery. Lundstrom et al. (8) proposed operation on asymptomatic or barely symptomatic patients with CCTGA and cardiac enlargement due to systemic ventricular volume overload. Two surgical approaches can be envisioned on the basis of the age of the patient at presentation. A classical approach consisting of early repair of lesions that overload the systemic RV appears well suited for older patients, as in our cohort. We propose to operate in a timely manner to keep the SVEF ≥40%. For patients presenting in early childhood, an anatomic repair, the double-switch operation, has yielded promising results (29). Adults, however, are much less likely to achieve anatomic repair (30), and patients with SAVV regurgitation have a poorer outcome (31). Whether an early double-switch operation confers long-term benefits over a classical strategy remains unknown.

Study limitations. Our study is retrospective. The small number of patients and events (11 deaths) confined us to a univariate analysis for identifying risk factors for late mortality. The small sample size also makes the multiple regression solution unstable. Our findings may not apply to all practices because our institution benefits from experience in congenital cardiology and cardiac surgery. The SVEF was predominantly estimated by echocardiography, and we assumed that SVEFs from multiple modalities were comparable. SVEF is dependent on the loading conditions of the ventricle and may not be the optimal criterion for ventricular function. Follow-up appeared more scrupulous in patients with systemic ventricular dysfunction, and thus events may have been missed in patients with better ventricular function. Our cohort does not allow us to evaluate the effects of cardiac resynchronization therapy and the Maze procedure in CCTGA patients.

Conclusions

More CCTGA patients undergoing SAVV replacement survive or remain free of cardiac transplantation with a pre-operative SVEF ≥40%. Long-term preservation of systemic ventricular function is also more likely with a pre-operative SVEF ≥40%. Any pre-operative atrial fibrillation and an SPVSP ≥50 mm Hg are risks factors for late mortality or cardiac transplantation. Patients with CCTGA should be scrutinized for the presence of SAVV regurgitation, systemic ventricular dysfunction, and a high SPVSP. Consideration should be given to SAVV replacement before the SVEF falls below 40% or the SPVSP rises above 50 mm Hg.

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Key Words: congenitally corrected transposition of the great arteries ■ ejection fraction ■ pulmonary pressure ■ tricuspid valve replacement ■ ventricular function.