Outcomes of treatment pathways in 240 patients with congenitally corrected transposition of great arteries

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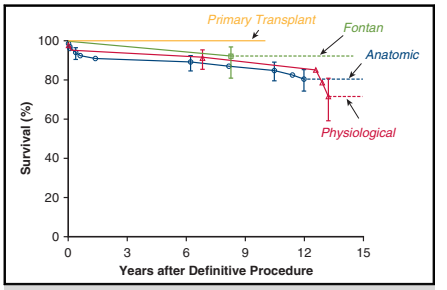
ABSTRACT

Objective: Congenitally corrected transposition of the great arteries (ccTGA) encompasses a diverse morphologic cohort, for which multiple treatment pathways exist. Understanding surgical outcomes among various pathways and their determinants are challenged by limited sample size and follow-up, and heterogeneity. We sought to investigate these questions with a large cohort of ccTGA patients presenting at different ages and representing the full therapeutic spectrum.

Methods: Retrospective review of 240 patients diagnosed with ccTGA from Cleveland Clinic coupled with prospective cross-sectional follow-up. Forty-six patients whose definitive procedure was completed elsewhere were excluded. Time-related survival was described among treatment pathways using actuarial, time-varying covariate, and competing risks analyses. Temporal trends in longitudinal valve and ventricular function were assessed using nonlinear mixed-effects models.

Results: Median follow-up was 10 years. Seventy-nine patients with ccTGA underwent anatomic repair, 45 physiologic repair, 24 Fontan palliation, and 6 primary transplant. Forty patients managed expectantly had excellent long-term survival when considered from time of presentation, but benefited from failures captured following transition to physiologic repair or transplant. Morphologic right ventricular dysfunction after physiologic repair increased from 68% to 85% after 5 years, whereas morphologic left ventricular function was stable in anatomic repair, especially with early surgery. Transplant-free survival at 15 years for anatomic and physiologic repair was 80% and 71%, respectively.

Conclusions: Early anatomic repair may be preferable to physiologic repair for select ccTGA patients. Late attrition after physiologic repair represents failure of expectant management and progressive tricuspid valve and morphologic right ventricular dysfunction compared with anatomic repair, where morphologic left ventricular function is relatively preserved. (J Thorac Cardiovasc Surg 2021;161:1080-93)



ccTGA treatment pathways and survival for early anatomic versus physiologic repairs.

CENTRAL MESSAGE

Early anatomic repair remains our preference because physiologic repairs for patient with ccTGA are associated with RV failure despite TV interventions.

PERSPECTIVE

In this large series of patients with ccTGA, early anatomic repair fares better than physiologic repair. Patients managed expectantly show what appears to be excellent survival, but must be viewed in light of failures captured following transition to other groups. Physiologic repair is compromised by progressive RV dysfunction despite subsequent TV interventions and attrition that escalates at 12 years postrepair.

See Commentaries on pages 1094 and 1095.

Current strategies for the management of congenitally corrected transposition of the great arteries (ccTGA) include expectant management, physiologic repair, anatomic repair, single ventricle repair, and primary heart transplant.[1] Physiologic repair addresses only the associated defects while keeping the morphologic right ventricle (mRV) as the systemic ventricle. Anatomic repair corrects atrioventricular and ventriculoarterial discordance and the associated defects, making the morphologic left ventricle (mLV) the systemic ventricle.[2-9] The natural history of unrepaired, isolated ccTGA and modified history after physiological repair may eventuate in progressive mRV failure and associated

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Abbreviations and Acronyms

ccTGA = congenitally corrected transposition of the great arteries
mLV = morphologic left ventricle
MRI = magnetic resonance imaging
mRV = morphologic right ventricle
PTx = primary transplant
TV = tricuspid valve
VSD = ventricular septal defect

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tricuspid regurgitation.[2] However, the patients most at risk for mRV and tricuspid valve (TV) dysfunction and the time course for development of these sequelae are unclear. Due to the rarity, the uncertain natural history, and the heterogeneity of associated lesions, there is great variability in timing of presentation, symptoms of this anomaly, and potential treatment approaches.[10] Decision making is further challenged because of the dearth of robust data comparing outcomes for all available treatment pathways and the paucity of long-term prospective follow up.[2,3,8,11]

In this study, we aimed to address these critical knowledge gaps by tracing outcomes of a large, single-center series of ccTGA patients with prospective cross-sectional follow-up, and describing factors that lead to impaired time-related survival, valvular function, and ventricular function.

METHODS

Population

From 1995 to 2000, 240 patients with ccTGA were treated at Cleveland Clinic. Comprehensive medical record review confirmed the diagnosis of ccTGA and chronicled past clinical history. Patients who had either a definitive physiologic repair, anatomic repair, Fontan palliation, or primary transplant (PTx) at an outside hospital before presentation were described, but were excluded from all further analyses. The cohort was divided into 5 groups according to definitive procedure: anatomic repair (arterial switch with atrial switch, Senning or Mustard, arterial switch with hemi-Mustard/Senning and bidirectional Glenn, and atrial switch/Rastelli), Fontan palliation, physiologic repair (defined as any cardiac surgical procedure except permanent pacemaker placement in which the mRV was maintained as the systemic ventricle), and primary heart transplant (no other surgical intervention before transplant, excluding permanent pacemakers). A noninterventional group (patients with no surgery/interventions or patients with only permanent pacemaker placement) was also defined.

Data Collection and Follow-up

Review of each patient's medical records, including operative reports, diagnostic reports, and outpatient clinic notes, was manually performed to obtain demographic information, associated lesions, and surgical history. Hemodynamic and anatomic characteristic were gathered from echocardiograms, catheterization, magnetic resonance imaging (MRI), and cardiac computed tomography reports at baseline, preoperatively, and postoperatively. For each operation, perioperative imaging studies were gathered at all available time points, including immediately postoperatively, before hospital discharge, and echocardiogram at time of prospective cross-sectional follow-up. In some cases, the short-term and long-term imaging reports were the same for a given patient. When adequate images were available, protocolized echocardiographic review was performed by ACGME-accredited fellows in pediatric cardiology and faculty (J.K., S.B., and R.K.). One hundred fifty-nine echocardiograms containing all 6 variables of interest were available for 75 anatomic repair patients (95% of the cohort). Median follow-up time was 9 days with 25% of the echocardiograms obtained after 4 years and 10% after 10 years (range, 1 day-24 years). Eighty-four echocardiograms containing all 6 variables of interest were available for 40 physiologic repair patients (93% of the cohort). Median follow-up time was 10.5 months with 25% of echocardiograms obtained after 7.7 years; 10% were obtained after 12 years (range, 1 day-28 years). Figure E1, *A* and *B*, shows available echocardiographic data over time for the anatomic repair group and the physiologic repair group. We performed a cross-sectional follow-up of the entire cohort via patient record review and telephone interviews using a standardized questionnaire. Median follow-up was 10 years with 10% followed more than 21 years since presentation. A total of 2589 patient years were available for analysis (Figure E2). The study was approved by Cleveland Clinic Institutional Review Board, with patient consent waived, except for consent for follow-up (IRB# 19-935).

Statistical Methods

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R software version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are summarized as mean ± standard deviation or as equivalent 15th, 50th (median), and 85th percentiles when distribution of values is skewed. Categorical data are summarized by frequencies and percentages.

Postoperative echocardiograms were analyzed longitudinally with a nonlinear multiphase mixed-effects cumulative/binary logistics regression model.[12] The model was implemented using PROC NLMIXED (in SAS). Prevalence of valvular regurgitation or ventricular dysfunction over time was then estimated by averaging the patient-specific profiles. Note that because of low frequency, higher grades (more than mild) of valvular regurgitation or ventricular dysfunction were collapsed into a binary variable (dysfunction or no dysfunction). Focused univariate analyses were performed by including age at repair or pulmonary trunk band as a covariate in the mixed-effects model.

Time zeroes of time-related analyses were time of presentation at Cleveland Clinic and time of definitive procedure. Nonparametric survival estimates used the Kaplan-Meier method. Focused univariate analyses were performed by stratifying the Kaplan-Meier estimates by different age groups, pulmonary trunk band placement, or TV intervention. Because we anticipated that certain patient outcomes, including survival and reintervention, might be biased in favor of the expectantly managed group (including time-related outcomes following definitive procedure), we performed 2 analyses to account for the transition from this group to other procedural groups. First, in the analysis of survival after presentation stratified by definite procedure, definitive procedures were treated as time-varying covariates. For this analysis, at time zero all the patients are in the nonintervention group and were censored at the time of definitive procedure, moving into respective definitive procedure groups. Parametric multiphase hazard model assessed the unadjusted effect of time varying definitive procedures on survival after presentation.[13] An extended version of Kaplan-Meier estimates[14] assessed the effect of time varying covariates on survival after presentation, nonparametrically.

CONG

Second, to demonstrate the prevalence of transition to either physiologic repair or primary transplant, competing risk analysis was performed to estimate transition probability into these 2 end-states from the state of no surgery, after adjusting for the competing risk of death before these 2 procedures. Transition probability to each state was estimated by the nonparametric product limit method.[15] Simultaneous operative transition probability (cumulative incidence function) from the category alive without procedures into each of the 3 categories were calculated by integrating the cause-specific parametric hazards functions.[12,13]

RESULTS

Description of Entire Cohort

Distribution and overall management of the cohort is illustrated in the flow chart in Figure 1. Median age at presentation was 8.5 years (15th, 85th percentile, 0.38, 41 years). Patient demographic and procedure characteristics, including associated lesions for each of the surgical pathways, are shown in Table 1.

Time to definitive repair differed among the 4 surgical groups, which reflects the variable natural history and proactive triage to anatomic repair for patients with suitable morphology. Early anatomic repair was preferred in patients in 2 distinct groups: those with well-functioning atrioventricular valves (less-than-moderate regurgitation and nonstraddling valves) with good biventricular function and normal systemic and pulmonary venous anatomy, and those with aforementioned features who had cyanosis and required initial palliation to augment pulmonary blood flow; these patients would ideally receive an aortopulmonary shunt followed by anatomic repair.

Median chronological age for anatomic repair was 2.4 years (15th, 85th percentile, 0.71, 7.4 years), 25 years (15th, 85th percentile, 1.4, 56 years) for physiologic repair, 4.3 years (15th, 85th percentile, 2.9, 9.6 years) for Fontan palliation, and 46 years (15th, 85th percentile, 34, 73 years) for PTx (Table 1 and Figure 2, *A*).

Description of Anatomic Repair Group

Patients reached anatomic repair via multiple pathways (Table E1 and Figure 2, *B*); 28 (35%) received a pulmonary trunk band at a median age of 9 months. The comparably lower prevalence of preparatory banding reflects our center's preference for primary anatomic repair at an earlier age. Two patients had multiple band tightening procedures and 6 underwent pulmonary trunk banding concomitant with other procedures. Reasons for banding among the youngest infants were for palliation of heart failure, mitigation of tricuspid regurgitation, and mLV retraining in anticipation for anatomic repair. Other preparatory procedures were performed in 39 patients. Twelve patients underwent primary anatomic repair without any prior surgery. Patients who had pulmonary trunk band underwent anatomic repair at a later age (median, 4.9 years) than those without initial banding (median, 2.4 years). The majority of patients in our series undergoing retraining achieved increases in

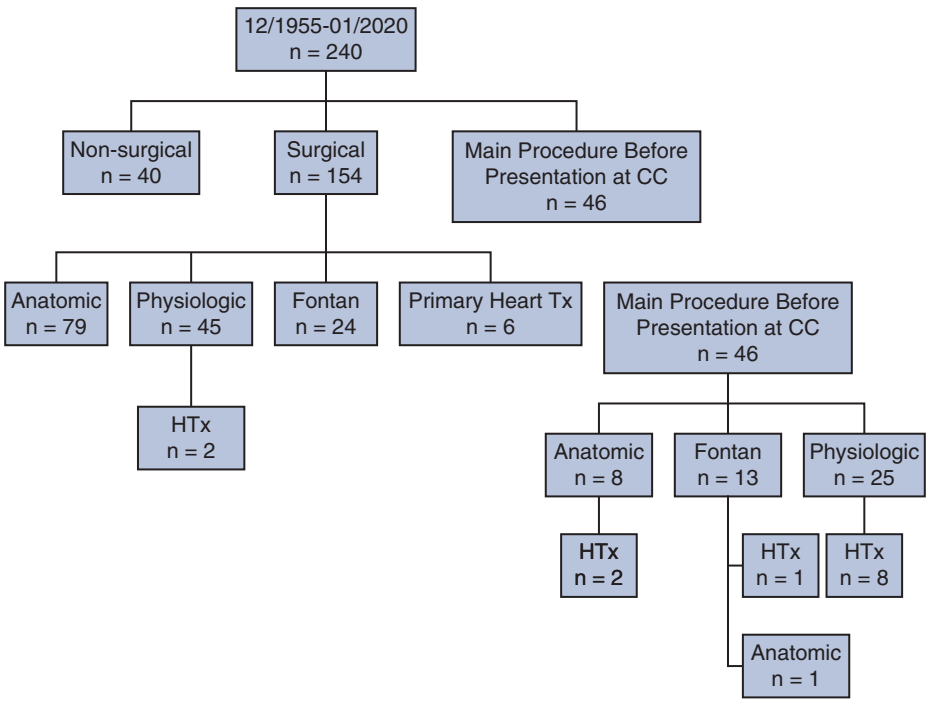

FIGURE 1. Patient flow chart of cohort including 240 congenitally corrected transposition of the great arteries patients and distribution of their definitive pathways. *CC*, Cleveland Clinic; *Htx*, heart transplant.

TABLE 1. Procedure details for the population segregated by repair type

Patient characteristic	Anatomic repair (n = 79)	Physiologic repair (n = 45)	Fontan palliation (n = 24)	Primary transplant (n = 6)	Nonsurgical (n = 40)
Female	28 (35)	12 (27)	8 (33)	2 (33)	21 (53)
Age at presentation (y)	1.6 (0.29, 5.9)	23 (1.0, 55)	0.08 (0.01, 5.0)	42 (31, 71)	35 (2.4, 60)
Age at definitive procedure (y)	2.4 (0.71, 7.4)	25 (1.4, 56)	4.3 (2.9, 9.6)	46 (34, 73)	N/A
Associated lesions					
VSD	73 (92.4)	17 (37.8)	12 (50.0)	2 (33.3)	15 (37.5)
ASD	16 (20.2)	5 (11.1)	6 (25.0)	1 (16.7)	2 (5.0)
CoA	6 (7.6)	4 (8.9)	3 (12.5)	0	0
Double outlet RV	10 (12.6)	1 (2.2)	5 (20.8)	0	0
Tricuspid regurgitation	23 (29.1)	17 (37.7)	0	0	2 (5.0)
Overriding tricuspid valve	2 (2.5)	1 (2.2)	1 (4.2)	0	0
Ebstein anomaly	7 (8.9)	3 (6.7)	1 (4.2)	0	0
Tricuspid valve atresia	0	2 (4.4)	2 (8.3)	0	0
Pulmonary atresia	16 (20.3)	3 (6.6)	4 (16.7)	0	1 (2.5)
Pulmonary stenosis, subvalvular	15 (19.0)	2 (4.4)	6 (25.0)	1 (16.7)	7 (17.5)
Pulmonary stenosis, valvular	20 (25.3)	7 (16.3)	10 (41.7)	1 (16.7)	5 (12.5)
Single ventricle*	1 (1.3)	4 (8.9)	15 (62.5)	0	0
Dextrocardia	24 (30.4)	5 (11.1)	8 (33.3)	2 (33.3)	7 (17.5)
Situs inversus	4 (5.1)	2 (4.4)	0	2 (33.3)	2 (5.0)

Values are presented as n (%) or median (15th, 85th percentiles). *N/A*, Not applicable, *VSD*, ventricular septal defect; *ASD*, atrial septal defect; *CoA*, coarctation of the aorta; *RV*, right ventricle. *Includes single ventricle-aortic valve atresia, hypoplastic left heart syndrome, single ventricle (double inlet left ventricle), single ventricle (double outlet RV), hypoplastic left ventricle, and overriding tricuspid valve.

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mLV pressures to 90% systemic with no more than mild–moderate decrease in mLV function.

Description of Physiologic Repair Group

Physiologic repair patients underwent a variety of interventions after definitive repair, including postrepair Glenn shunts, TV interventions, ventricular septal defect (VSD) closures and valvuloplasty (Table E1).

Description of Fontan Group

The majority of patients in this pathway (62%) had only 1 functional ventricle. Other associated lesions are shown in Table 1. Prerepair procedures included pulmonary trunk banding (38%), aortopulmonary shunts (50%), and Glenn shunts (71%) (Table E1).

Morbidity for the Cohort

Pacemaker implant. Overall, 84 patients received a permanent pacemaker, 7 of whom were in the nonintervention group. Twenty-nine patients in the physiologic repair group received pacemakers, 19 (65.6%) considered iatrogenic in that they were placed for surgically induced complete heart block. Twenty-two patients in the anatomic repair group received pacemakers; 5 were implanted before their definitive procedure and 17 (77.2%) were iatrogenic. Two Fontan palliation patients received pacemakers after their definitive procedure. PTx patients had pacemakers implanted before transplant. Based on these numbers, the prevalence of native, noniatrogenic complete heart block was 29.8%.

Re-interventions. Re-intervention following definitive procedures, including transplant, occurred in 20 patients (Figure 1 and Table E1). Among anatomic repairs, 10 patients had revisions to correct sequel related to repair (2 TV interventions, 2 VSD closures or repatching, 6 revisions of the right ventricle to pulmonary artery conduit), and 2 underwent heart transplant. Ten patients in the physiologic repair group underwent transplant. One patient in the Fontan palliation group was transplanted, and another was converted to anatomic repair.

Time-Related Survival

Survival was considered from 2 time points to capture heterogeneity in timing of presentation that may affect candidacy for specific pathways.

Time-related survival after presentation. The first, time of presentation as time-zero, allows consideration of all pathways, including the nonintervention group. Survival for the entire cohort after presentation at 1 month, 1 year, 5 years, 10 years, 15 years, and 20 years were 99%, 96%, 90%, 87%, 80%, and 73% respectively (Figure E3). Survival after presentation in the nonintervention group was 99%, 99%, 97%, 94%, and 88% at 1 month, 1 year, 5 years, 10 years, and 20 years, respectively (Figure 3, *A*). Late-phase survival among anatomic repair and physiologic repair groups, when

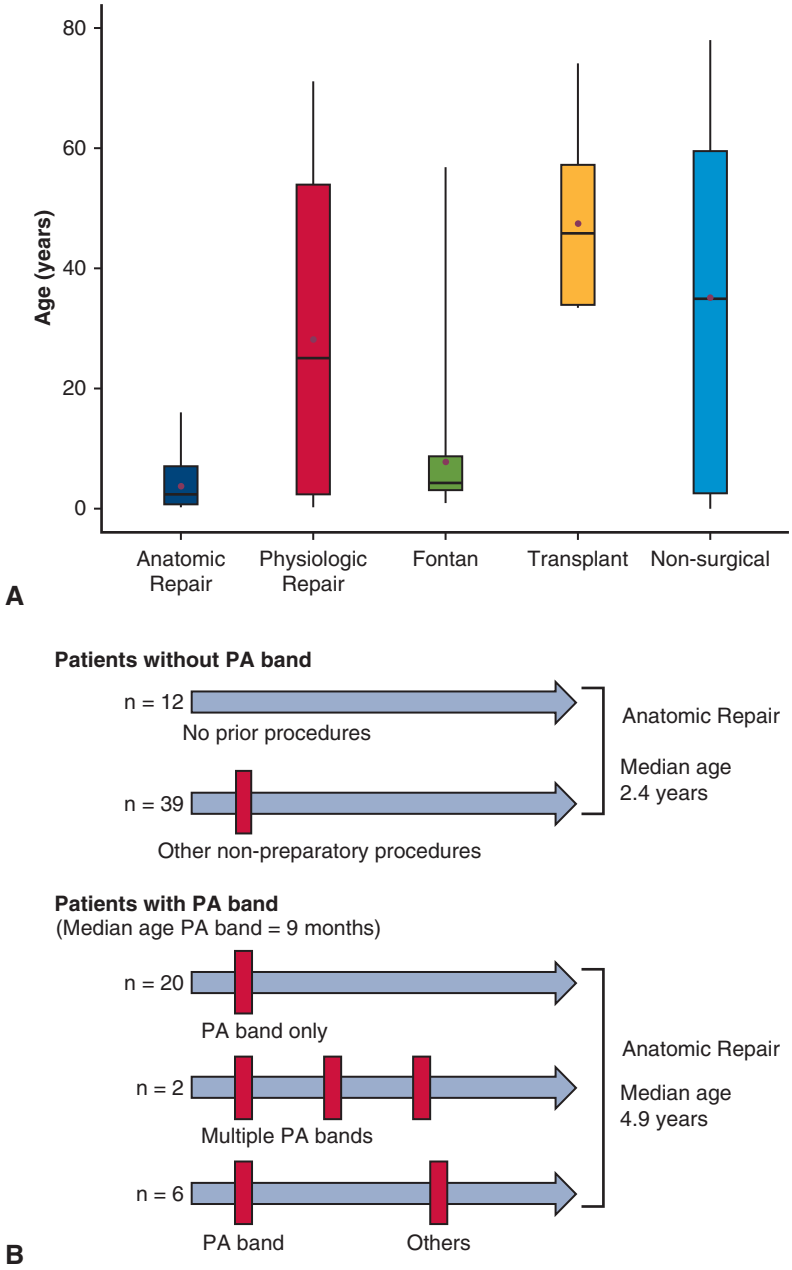


FIGURE 2. Effect of age at presentation on survival. A, Box-and-whisker plots displaying median age at presentation in years for all pathway groups (*cross bar*). *Box* depicts 15th to 85th percentiles, and *whiskers* extend from the minimum value to the maximum value with the red dot indicating the mean value. B, Various pathways to anatomic repair among those who underwent preparatory pulmonary trunk banding and those who had primary anatomic repair or underwent other palliative procedures. The median age was older among those having preparation of the morphologic left ventricle. *PA*, Pulmonary artery.

considered from time of presentation, was lower compared with the nonintervention group (Figure 3, *A*, and Table E2).

To further illustrate the transitions inherent in the nonintervention group, competing risks analysis demonstrated the prevalence of the competing events of death without any intervention, physiologic repair, and PTx (Figure 3, *C*). The Fontan and anatomic repairs were excluded from this analysis because they underwent anticipatory early surgery and therefore were not considered to be failures of expectant management. At 20 years following presentation, 56% of patients had transitioned to physiologic repair, 27% remained in the nonintervention group, 8% underwent primary transplant, and 9% had died. There was a steady

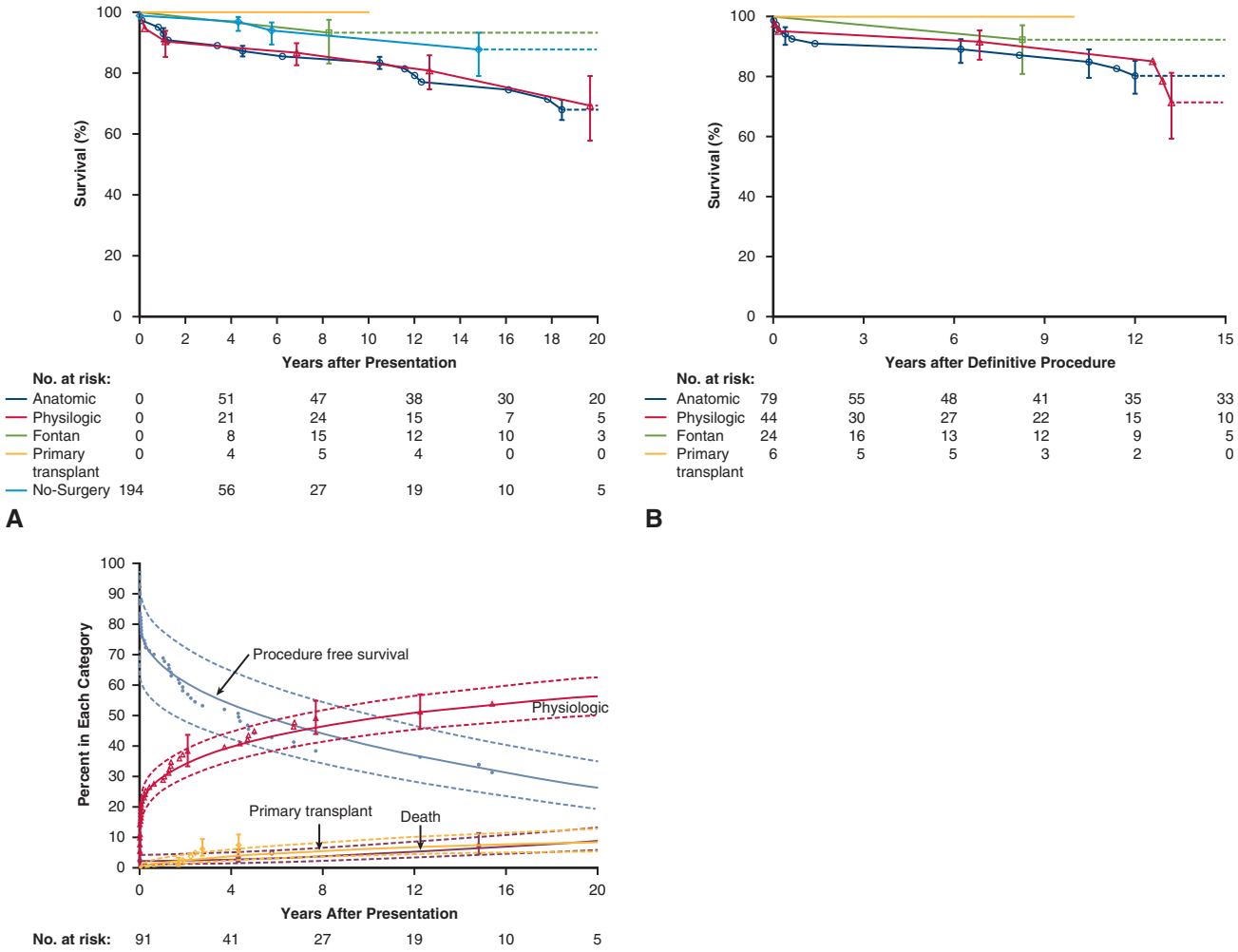


FIGURE 3. Transplant-free survival after presentation and after definitive procedures. *Symbols* are nonparametric estimates enclosed within 68% confidence bars. Number of patients at risk at various time points are given under the *x*-axis. A, Transplant-free survival after presentation at Cleveland Clinic. Note that, in this analysis, the definitive procedures are considered as time-varying covariates and the nonparametric estimates were obtained by an extended Kaplan-Meier estimate.[13] Note that at time zero all the patients are in the nonsurgery group and were censored at the time of definitive procedure, moving into respective definitive procedure groups. B, Transplant-free survival after definitive procedures. (Transplant = Primary Transplant). C, Competing risks plot for only those patients having either no intervention, physiologic repair, or primary transplant. All patients begin in the noninterventional group at time of presentation and transition to primarily physiologic repair or transplant or die before reaching 1 of these 2 procedures. At 20 years, 56% of patients had physiologic repair, 27% remained without intervention, 8.4% had primary transplant, and 9% had died. Colored lines demonstrate these transitions and probability of each of these three mutually exclusive events. Dashed lines followed by solid lines depict absence of events during this time frame that alters the nonparametric estimates.

transition to the physiologic repair group across time, which escalated in the first 5 years following presentation.

Time-related survival after definitive repair. The second, time of definitive repair as time zero, considered only those patients who underwent definitive repair. Midterm survival after definitive repair was similar among the 4 surgical pathways (log-rank $P = .9$) (Figure 3, *B*). However, attrition among physiologic repair patients occurred at approximately 12 years after repair, compared the more stable survival curve seen in anatomic repair. Survival for patients who underwent anatomic repair was 99%, 93%, 91%, and 80%, and that after physiologic repair was 98%, 95%, 95%, and 71%, respectively ($P = .09$).

Risk Factors for Death Among Anatomic and Physiologic Repairs

Among anatomic repair patients, prior pulmonary trunk banding and late age at anatomic repair, had similar survival (Figure 4, *A* and *B*). Among physiologic repairs, TV

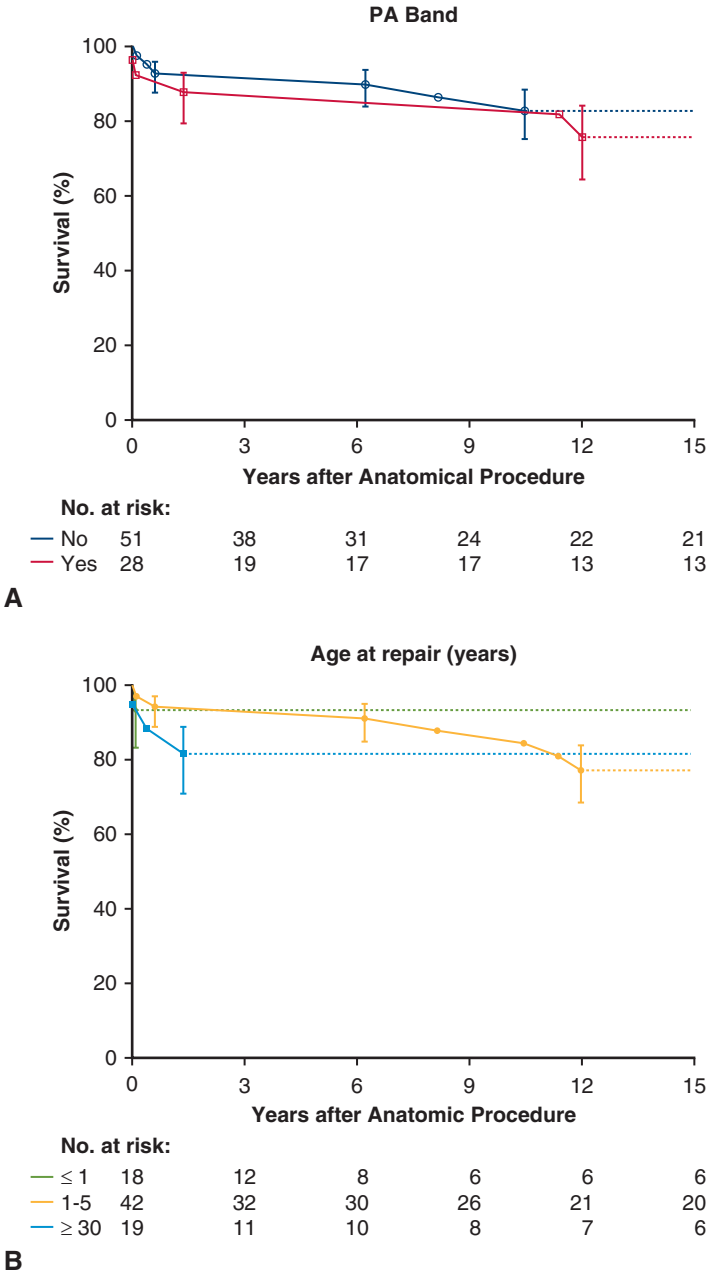


FIGURE 4. Overall survival after anatomic repair. *Symbols* are Kaplan-Meier nonparametric estimates enclosed within 68% confidence bars. Number of patients at risk at various time points are given under the *x*-axis. A, Overall survival after anatomic repair stratified by pulmonary artery (*PA*) band versus no PA band before anatomic repair (log-rank $P = .9$). B, Overall survival after anatomic repair stratified by age at repair (log-rank $P = .5$). *Colored lines* show the survival after anatomical repair stratified by age groups at repair. *Dashed lines* followed by *solid lines* depict absence of events during this time frame that alters the nonparametric estimates. Note that patients who were younger at repair tended to have improved survival.

intervention (n = 6) was not associated with improved survival compared with those who did not have TV intervention (log-rank $P > .9$) (Figure E4), although this analysis does not account for the functional status of the mRV at the time of TV intervention, which may influence the benefit gained from restoration of TV competence.

Valve and Ventricular Function Following Anatomic Repair

Trajectory of atrioventricular valve and systemic ventricle function differed among the anatomic and physiologic repair groups. After anatomic repair, mitral valve regurgitation increased slightly initially but stabilized and remained constant thereafter

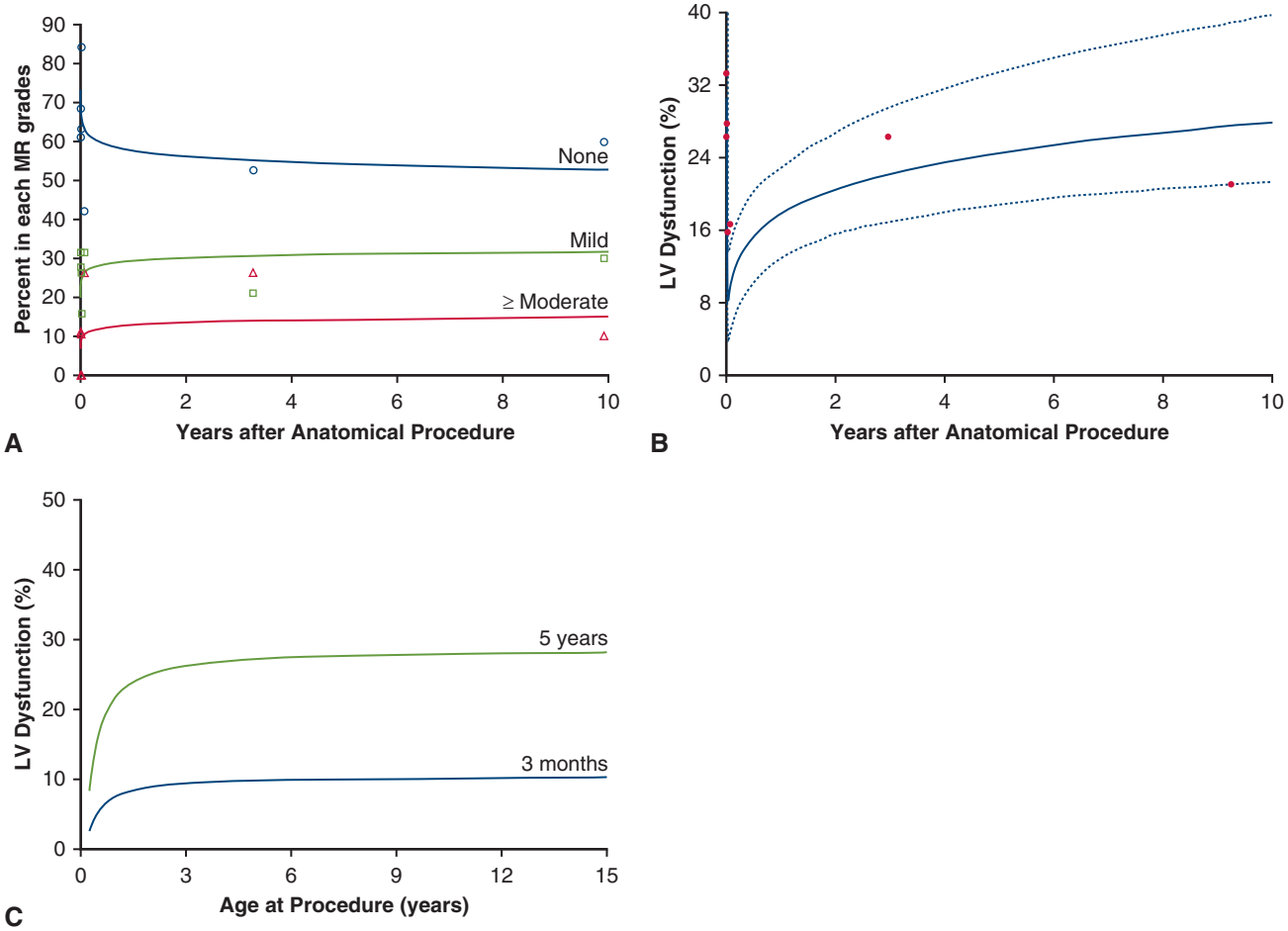


FIGURE 5. Fate of mitral valve and morphologic left ventricle (*mLV*) in anatomic repair. A, Temporal trend of prevalence of postoperative mitral regurgitation (*MR*) grades. *Solid lines* represent parametric estimates of patients in each grade over time after the procedure. *Symbols* represent data groups (without regard to repeated measurements) within time frame to provide a crude verification of model fit. B, Temporal trend of prevalence mLV dysfunction after anatomic repair. *Solid lines* represent parametric estimates of patients with mLV dysfunction over time after the procedure enclosed within a 68% bootstrap percentile confidence interval. *Symbols* represent data groups (without regard to repeated measurements) within time frame to provide a crude verification of model fit. C, mLV dysfunction and age at the time of anatomic repair. *Solid lines* are nomograms obtained by solving a univariate longitudinal model at 3 months and at 5 years postprocedure.

(Figure 5, *A*). mLV dysfunction initially improved then increased with subsequent stabilization such that only 28% of patients had any degree of dysfunction 10-years after anatomic repair (Figure 5, *B*). Earlier age of anatomic repair was related to mLV dysfunction (Figure 5, *C*).

Valvular and Ventricular Function After Physiologic Repair

Although the percentage of patients with TV regurgitation increased after physiologic repair, this proportion of patients with moderate or greater tricuspid regurgitation then decreased (decussation in curves) at approximately 4 years, reflecting the success of TV interventions to correct tricuspid regurgitation (Figure 6, *A*). Ten (22%) patients underwent TV repair and replacements during the period of available follow-up. Six had TV repair at a mean age of 28 years, approximately 3 years after physiologic repair. The remaining 4 patients underwent TV replacement at a mean age of 29 years, approximately 4 years after physiologic repair (Table E1). Notably, mRV dysfunction increased despite surgical intervention to mitigate tricuspid regurgitation: 84% of physiologic repair patients had right ventricular dysfunction after 10 years (Figure 6, *B*).

DISCUSSION

Our study illustrates the complexities inherent in studying this anatomic entity and, we believe, may suggest the need for protocolized, multi-institutional prospective

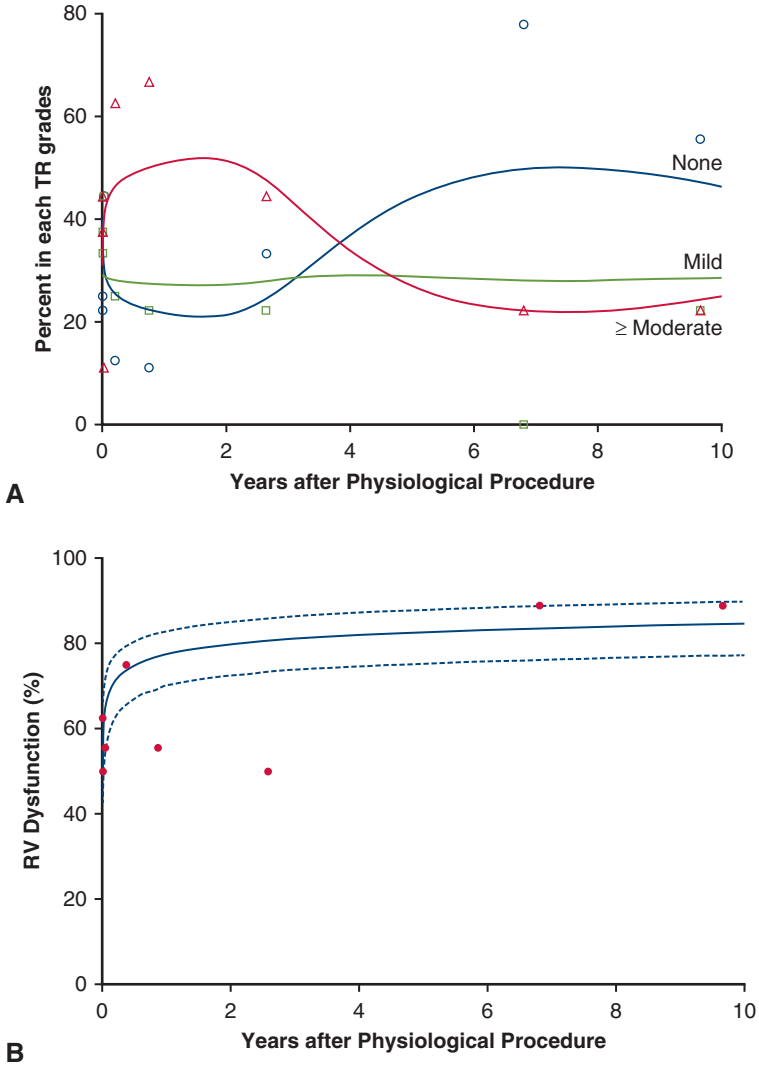


FIGURE 6. Fate of the tricuspid valve and morphologic right ventricle (*RV*) after physiologic repair. A, Temporal trend of tricuspid regurgitation (*TR*) grades after physiologic repair. Format as in Figure 5, *A*. B, Temporal trend of RV dysfunction after physiologic repair. Format as in Figure 5, *B*.

study. Our data demonstrate several key points: early anatomic repair may provide long-term benefits in terms of preservation of mLV function, TV interventions among physiologic repair patients does not improve mRV function and does not appreciably improve survival, Fontan pathways have excellent midterm outcomes and therefore should not be discarded as a viable option for patients with a single atrioventricular valve (ie, tricuspid atresia) or 1 ventricle (Video 1).

Long-term survival among the anatomic repair patients in our series (81% at 10 years) was better than that reported in other published series,[16-20] and was comparable to those patients amenable to nonintervention or expectant management. Our data demonstrate the rates of transition toward primarily physiologic repairs and transplant among patients who were managed expectantly and show the complexities in analyses required to more fairly compare outcomes in this population. Better anatomic repair survival at our center may reflect our preference for earlier anatomic repair (median, 2.3 years) that reduced the need for mLV retraining and resulted in less decline in mLV function over time (Table E3). Mainwaring and colleagues[21] demonstrated that preparatory pulmonary artery banding may, in some cases, lead to a maladaptive hypertrophic response out of proportion to the pressure-load applied—a response that undermines the success of mLV retraining.[21] Specific criteria that have been applied to ccTGA patients to predict successful immediate and long-term mLV retraining include an increase in left ventricle mass to 50 g/m^2, mLV end diastolic pressure <12 mm Hg,

VIDEO 1. Drs Barrios and Karamlou, the first and senior author, discuss the key messages from the manuscript in this short 5-minute segment. Video available at: https://www.jtcvs.org/article/S0022-5223(20)33341-9/fulltext.

mild or less mitral regurgitation, and mLV pressures that reach 90% systemic.[21] Success of mLV retraining in our series was good, with the majority of patients achieving mLV pressures of 90% systemic with no more than mild–moderate decrease in mLV function. Unfortunately, data on mLV mass response to pressure loading over time were not available in our early cohort except in 15 patients, and these were not standardized nor acquired with MRI. Currently, we utilize preoperative MRI to assess the mLV mass response to pulmonary trunk banding, but have had at least midterm success in patients not reaching 50 g/m^2, suggesting that this may not represent an absolute contraindication. Phenotypic adaptive responses within the mLV clearly have distinct patterns, some of which are undoubtedly motivated by age, and these require further study. We were not able to demonstrate a specific harm to patients undergoing initial pulmonary trunk banding, but this may be due to the small number of patients that underwent banding. It is tempting, therefore, to suggest that infants should undergo anticipatory anatomic repair based on our data, but, given the arguably equivalent survival in the nonintervention patients, we are reticent to recommend this except among the truly ideal anatomic candidates or those with associated lesions necessitating other procedures (ie, pulmonary stenosis or large VSD). Unfortunately, the allocation of risk among nonintervention patients remains unclear. The quasi-lead-time bias inherent in those managed expectantly such that they transition to primarily nonanatomic repair pathways once they develop hemodynamically significant lesions, confounds fair head-to-head comparison among groups.

What can be gleaned from this study to inform selection among surgical treatment pathways? Is there validity in comparing survival among the physiologic and the anatomic repair groups given that candidacy for anatomic repair is defined by a relatively narrow age-window and by morphologic criteria? Patients with physiologic repair had equivalent early and midterm survival to those having anatomic repair, but the curves diverged around 12 years postrepair such that overall survival was lower among physiologic repair patients (71% at 15 years). Trajectories of TV dysfunction and mRV dysfunction reflected the fallibilities of physiologic repair that limit durability. We noted an improvement in TV function around 4 years following physiologic repairs that were due to surgical interventions to correct tricuspid insufficiency. However, despite the apparent successful reduction in tricuspid regurgitation, the mRV continued to deteriorate over time. Further, reductions in tricuspid regurgitation did not translate into a survival benefit among physiologic repair patients who underwent TV interventions versus those who did not—a finding consistently shown in previous studies.[22] That the physiologic repair group also had the highest prevalence of transplant than any other pathway infers an inability to rescue patients in which systemic mRV function begins to decline. Therefore, although direct comparisons are challenged by the inherent differences in anatomy and age that may eliminate candidacy for specific pathways (eg, anatomic repair beyond late childhood), the long-term attrition among the physiologic repair patients cannot be discounted. The presence of underlying physiologic correlates we have demonstrated together with the higher prevalence of transplant, support our recommendation that early anatomic repair, when possible, may still be the preferred surgical therapy for patients with ccTGA.[8,19,20]

Although not a major focus of this study, we elected to include patients undergoing Fontan for several reasons. First, although some anatomic cases (tricuspid atresia) are clearly candidates for only Fontan palliation, other single-ventricle anatomies present in our cohort underwent both anatomic and physiologic repairs, underscoring the discretionary triage that occurs even within 1 center. Second, thresholds for biventricular repair are dynamic. Criteria for Fontan in cases where there are 2 atrioventricular valves and 2 ventricles are not absolute and subject to surgeon and center bias such that patients with straddling tricuspid valves or Ebstein anomaly may be triaged to Fontan by some, but to septation by others. Third, Fontan pathway may be leveraged by patients in both the anatomic and physiologic repair groups in the event of a failed biventricular strategy (ie, crossovers). Finally, although our group advocates for biventricular repair if anatomically feasible, good outcomes of the Fontan group, although perhaps not surprising, attest to the utility of single ventricle repair in select ccTGA phenotypes.

Limitations

The limitations of this study include the bias associated with patient selection for each of the pathways based on candidacy and anatomy, as well as the retrospective nature of this study. Additionally, the hemodynamic data collected

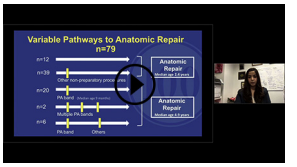
in this study are limited by poor echocardiographic images in some cases as well lack of optimum (and comparable) echocardiographic data for patients in the different groups. The current data were enhanced by dedicated off-line image review to obtain as much information as possible from existing studies rather than rely on abstraction from echocardiographic reports. Further, to improve available follow-up, we performed a prospective cross-sectional follow-up that included the entire cohort (median follow-up time 10 years), which did include clinical data and functional status. The discrepancy between median follow-up times for the physiologic repair and anatomic repair patients is <1 year (9 days vs 10 months), which should not skew results substantially given that survival for the anatomic repair group was excellent out to 5 years. Definitive procedure group-specific analyses are based on smaller sample size; hence, may lack statistical power to detect some possible associations. Finally, the heterogeneity in timing of presentation introduces bias in the analysis of outcomes and limits the comparability of the treatment pathways. Patients undergoing physiologic repairs are much older than those having anatomic repairs, an inevitable difference with perhaps more relevance given the potential benefit of younger age in the anatomic repair group. We acknowledge that our study cannot fairly inform the decision toward anticipatory anatomic repair given the excellent outcomes of the expectantly managed group. We are unable to embellish this dialogue further given that the denominator of the nonintervention group is unknown relative to the patients undergoing early operation and more importantly, patients move out of this group as they enter other pathways (such as physiologic repair or PTx). These transitions reduce the survival of the receiving groups and artificially increase the survival in the expectant management group. We attempted to address this fundamental problem by the creation of 2 different time-related survival analyses in which transition is considered as a time-varying covariable. An inception cohort study, which consider patients at the time of diagnosis of ccTGA, would facilitate identification of those candidates who will benefit from early surgical repair and those who may be followed expectantly.

CONCLUSIONS

The management of ccTGA is highly variable, reflecting both the anatomic heterogeneity of this condition and the wide age range at first contact. Our experience has good long-term survival (80% at 15 years), potentially related to earlier anatomic repair that decreases the prevalence and length of mLV retraining, and may mitigate mLV function decline. Physiologic repair is compromised by progressive right ventricle dysfunction despite subsequent TV interventions and attrition that escalates at 12 years postrepair. Although nonintervention or expectant management may have reasonable survival, this approach must be weighed against the long-term risk of failure and the transition to physiologic repair.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/20AM/Presentations/Outcomes%20and%20Their%20Determinants%20for.mp4.



Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: congenital, great vessels, outcomes, transposition

Discussion

Presenter: Dr Aisha Zia

Dr Glen S. Van Arsdell *(Los Angeles, Calif)*. Thank you for that clear presentation. This is a really complex topic. You have corrected transposition with no associated lesions. You have varying associated lesions, some that can lead to a need for a single-ventricle repair or a choice for a single-ventricle repair. And it's a rare lesion; that's 240 patients over 65 years. If you look at a prevalence, it's about 0.3% to 0.4% of all surgical cases.

So it's hard to come to the right answers, given the numbers of patients and the heterogeneity of presentation and treatment. You focus particularly on 80 anatomic corrections with the survival of just more than 80% at 10 to 12 years, and it was very equivalent to the physiologic repair survivals, although the age of presentation was remarkably different.

It's clear that our profession seems to have a bias to move toward anatomic repair over the past 20 years. Yet the results have not yielded what had been hoped. Contrast that to simple transposition, where anatomic repair delivered remarkably, and it delivered it across the world. The Toronto data that were presented at in Washington a few years back showed outcome curves that were essentially the same as yours, and there was a similar number of treatment patients in each arm since 2000 showing equivalent outcomes for anatomic and physiologic repairs.

What it demonstrated was that operative mortality wasn't really the issue. The issue was development of ventricular dysfunction over time. And interestingly enough, those patients who did not require any repair and who were not operated on had a 95% survival at 30 years. When you put all these things together, it tells us there's something different about corrected transposition. We can do accurate surgery; we can show that in the operating room. Early operative mortality is not the same as simple transposition, but it's not prohibitive. Yet we develop late heart failure and if we don't move on to death, there's risk of death, because we know ventricular dysfunction is a risk for mortality.

It leaves us to ask the question: Maybe we need to develop a perfect criteria for doing an anatomic correction, as with Fontan palliation. Kirkland developed the perfect Fontan criteria a number of years ago. So in that spirit, I ask: Were you able to gather any insights in what might have correlated to later failures? Things that have been shown, for example, have been bands versus no bands in preparation. Or development of heart block or not getting heart block.

Do you have any insights into that that you might share with us?

Dr Tara Karamlou *(Cleveland, Ohio)*. Thank you very much, Glen. I think we're going to tag-team this, given that Aisha did a fantastic job but hasn't spent years in congenital heart surgery. Even among an experienced study group such as our moderators and our discussant, we still have not come to a consensus as to how best to manage the collective anatomy

that defines congenitally corrected transposition.

What we can say from this series is that it is clear that the age at presentation as you mentioned is likely a critical factor in determining outcome. And in some cases it's going to be a determining factor because when the patients present, as in the physiologic repair group, they may be presenting at a time when their right ventricle is already failing or when their tricuspid valve is already a problem. So in some ways, the favoritism toward anatomic repair may be due to the anticipatory nature of those surgeries, in so far as they are planned. Regarding characteristics that may potentially improve the outcome of anatomic repair, our age at repair was slightly younger than the majority of series, although there are series where the median age approximates ours. This may be a reason for slightly better outcomes. However, we didn't have a huge event rate among this population; it is too small to look in detail at the demographic characteristics, including age, that may influence outcomes long-term.

With regard to retraining, what we can say about our group is that in general, our favoritism was to do early repair rather than put patients down or retraining pathway. If you looked at the Stanford data (and they are probably the group that has studied this in the most rigorous way), most patients followed a retraining pathway that was relatively predictable, with the caveat that some patients developed left ventricle hypertrophy that was out of proportion potentially to the pressure load that was applied, suggesting that certain phenotypic or even genetic components that may mediate the type of hypertrophic response actually was at play here.

Ultimately, we have a lot of data among our specialty collectively. I think synthesizing it into a cohesive message with small patient numbers that are usually treated at 1 center in a nonprospective fashion has hampered our ability to really answer the question about optimizing retraining that you're rightly posing. With regard to the arrhythmia issue, we have no data, but I think resynchronization therapy, QRS intervals, and looking at the morphology of the QRS could give us some guidance as to which patients may benefit, but in some ways that's rearranging furniture and I'm not sure that the durability of that technique is going to influence the overall outcome.

Dr Van Arsdell. I'll pose 2 more questions. You gave us outcomes for a perfect patient. What about the imperfect patient? Let's say you have a 2-year-old patient who presents with some mitral regurgitation, some mild ventricular dysfunction, but is a candidate for an upfront Rastelli Mustard.

How do you think about that patient? Should we be doing a double switch? What should we do—or do we not know? As a follow-up to that, given that we have this ongoing risk of development of ventricular failure, which seems to be in all series that follow this longitudinally (there may be some data out there that we don't know about, but at least in what's published): Do you think that we should be thinking about putting all these patients on prophylactic heart failure medications?

Dr Karamlou. Yeah, it's an interesting question. I think again, the most honest and transparent answer is that we don't know what the best modality is in terms of pathway for patients with imperfect anatomy. We can safely say that patients who have more-than-moderate mitral insufficiency or who have left ventricle dysfunction that it is moderate initially are probably not good candidates for anatomic pair.

However, if you look at our curves, an interesting point is that as valvular and ventricular function progressed, albeit slowly, but survival seemed to plateau, and that was an interesting finding to us. This was in contradistinction to the physiologic repairs where attrition seemed to mirror the trajectories of right ventricle dysfunction and the development of tricuspid regurgitation.

So again, not to avoid your question, but I think the best answer is: We don't know. I think prophylactic heart failure therapy is an interesting concept. It has been used successfully in single-ventricle patients. Some of the data on digoxin have been favorable, angiotensin-converting enzyme inhibitors, but the population of congenitally corrected transposition of the great arteries is so varied, it would probably take a prospective study for us to understand that.

Dr Van Arsdell. Thank you.

Dr Karamlou. Thank you, Glen.

Dr Kristine J. Guleserian *(Dallas, Tex)*. Aisha and Tara, 1 obvious question. We have a 65-year time period. Was there any era effect that you were able to observe, even though overall these numbers are small on an annual basis?

Dr Aisha Zia *(Cleveland, Ohio)*. More patients were operated on during the Roger Mee era, which was in 1995 to 2000. Before 1983, there were only 3 patients, and we lost them because they died and we were unable to include them in our cohort. We have done about 5 patients more recently, all of whom underwent double anatomic repair here.

There are definitely differences in approach and an era effect, but we did not specifically look at that because the preponderance of patients were done in an earlier era. Something to do in the upcoming study.

Dr Karamlou. The short answer is no, Kris, we weren't able to look at that.

Dr Guleserian. What is your management strategy for the neonate with corrected transposition who doesn't have

any significant valvular disease, valvular dysfunction, or ventricular dysfunction? Are you recommending neonatal repair or another pathway? How do we deal with these patients?

Dr Karamlou. I think it depends on the associated lesions, Kris. As you well know, if there's no ventricular septal defect, if there's no pulmonary stenosis, you might want to manage those patients differently. In a patient who's balanced, you could probably avoid doing things very early on, with the caveat that you may need to retrain them. An interesting thing to bring up that is somewhat provocative: If you look at David Quinn's data from 2008, patients who require retraining did better than patients who did not require retraining, and that is different among different studies. So I think it's a very interesting question: Do you band early, do you do nothing, or do you go ahead and do a double switch? My own bias, quite frankly, is based on the data that we have, it's very difficult to recommend a pre-emptive operation in a patient who may be balanced and who may be wonderful for many, many years.

Among the curves we didn't show because our time zero was intervention (therefore excluding the patients not receiving any therapy), was the nonintervention patients. The patients who despite their diagnosis seems to live a normal life (nearly), asymptomatic with very little restrictions on their exercise, and so on. We had 6 deaths only in our 46 medically managed patients.

It's hard to beat that. That's 15%, which is actually better than the anatomic repairs.

Dr Emile Bacha *(New York, NY).* That's actually a very, very important piece of information. The on-treatment arm, that's a hugely important arm. You could do nothing for that 4-year-old and let him be if he's asymptomatic.

Dr Karamlou. Absolutely, Emile.

Dr Bacha. A lot of cardiologists would argue that.

Dr Guleserian. Right, and I think when we talk to families, we have to include the nonmanagement strategy when we are offering management.

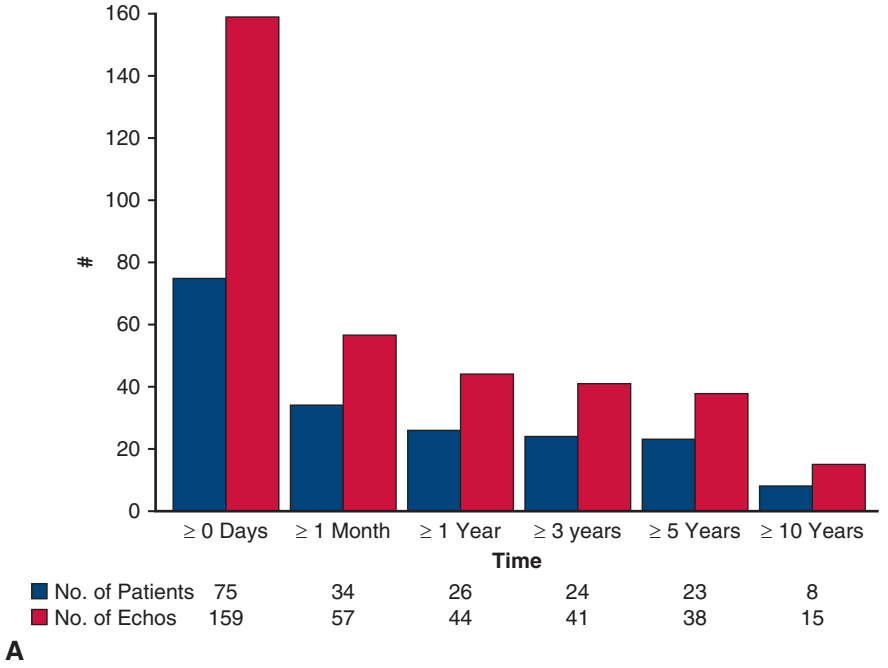
Dr Karamlou. I couldn't agree more. And I think, obviously we were little bit pressed due to some of our resources getting deployed to likely much more important things given the present circumstance, but this is something that we will definitely touch on in the manuscript.

I think Rohit Loomba and Andrew Redington's editorial that commented on Brizard's 2017 article was really prescient and very important and we have to have a very circumspect approach with a lesion in which the uncertainties are probably greater than the certainties.

Dr Guleserian. Well, thank you again for a wonderful presentation and best of luck in your pediatrics residency this summer. Great job.

Dr Zia. Thank you.

Dr Karamlou. She's fantastic.



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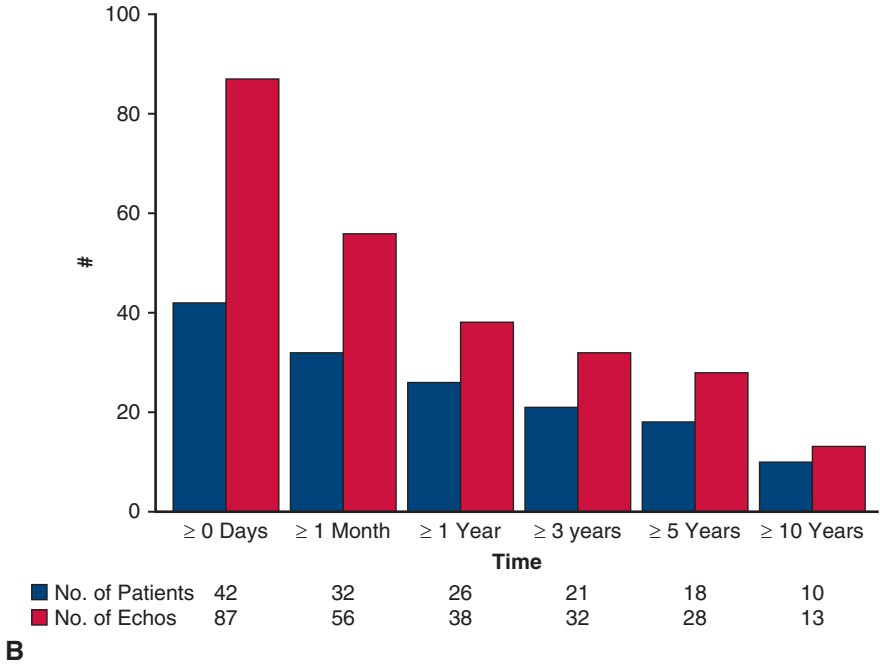

B

FIGURE E1. Echocardiographic data (*Echo*) collection over time. Number of patients with amount of available Echos at and beyond designated time points. A, Echo data collection after anatomic repair. B, Echo data collection after physiologic repair.

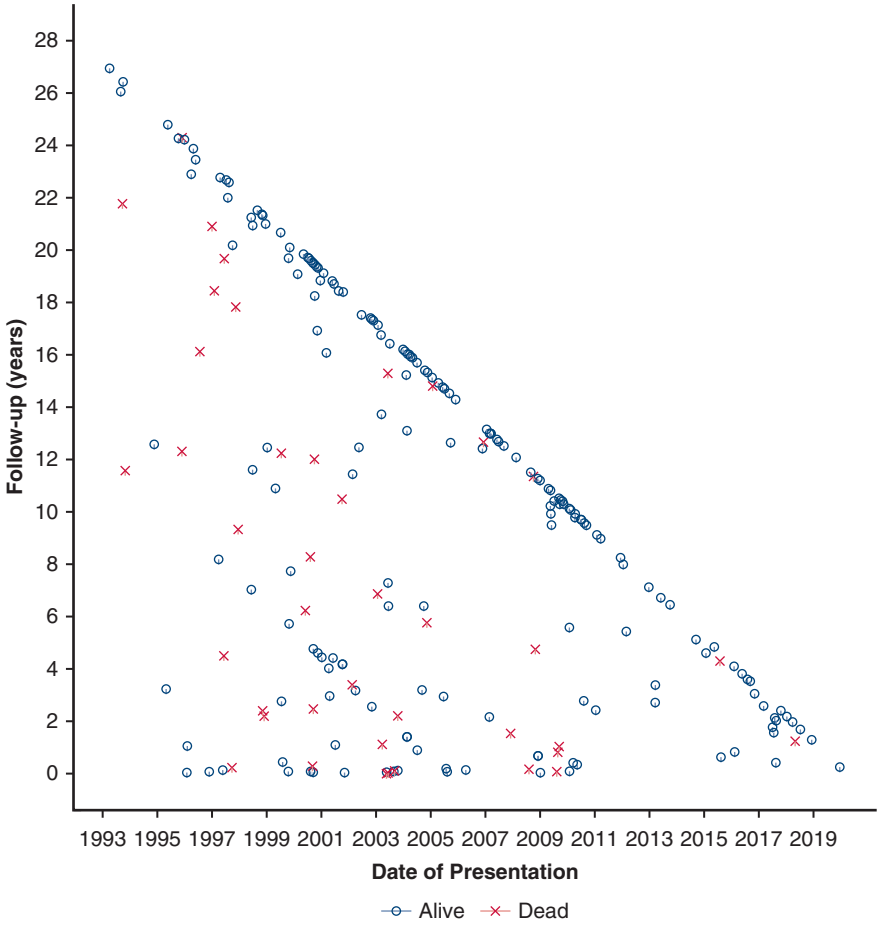

FIGURE E2. Goodness of follow-up of vital index. *Blue circles* depict the available maximum follow-up for alive patients and *red crosses* depicts the death of patients.

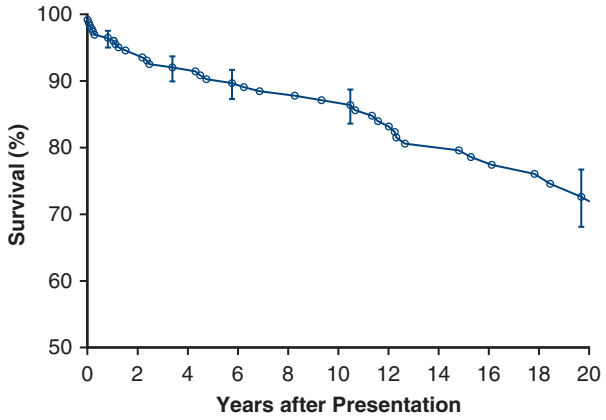

FIGURE E3. Overall survival after presentation. *Symbols* are Kaplan-Meier nonparametric estimates enclosed within 68% confidence bars.

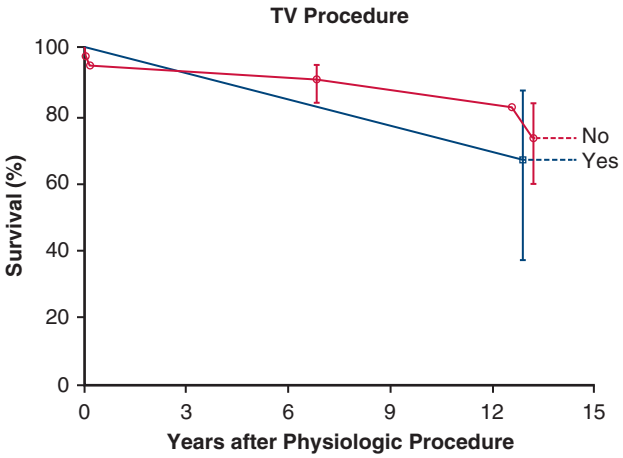

FIGURE E4. Survival after physiologic procedure stratified by tricuspid valve (*TV*) intervention. *Symbols* are Kaplan-Meier nonparametric estimates enclosed within 68% confidence bars.

TABLE E1. Procedures performed among physiologic, anatomic, and Fontan patients

Procedure	Anatomic repair	Physiologic repair	Fontan
Pulmonary artery banding: Pretreatment	28 (35)	7 (16)	9 (38)
Aortopulmonary shunt: Pretreatment	21 (27)	2 (4.4)	12 (50)
Glenn shunt: Pretreatment	5 (6.3)	1 (2.2)	17 (71)
Glenn shunt: Posttreatment	1 (1.3)	3 (6.7)	0
Tricuspid valve repair: Pretreatment	2 (2.5)	3 (6.7)	0
Tricuspid valve repair: Posttreatment	2 (2.5)	3 (6.7)	0
Tricuspid valve replacement: Pretreatment	0	2 (4.4)	0
Tricuspid valve replacement: Posttreatment	0	3 (6.7)	0
VSD closure: Pretreatment	2 (2.5)	10 (22)	0
VSD closure: Posttreatment	2 (2.5)	1 (2.2)	0
Coarctation repair: Pretreatment	5 (6.3)	3 (6.7)	0
RV to PA conduit: Pretreatment	6 (7.6)	1 (2.2)	0
Pulmonary valvotomy: Pretreatment	1 (1.3)	2 (4.4)	0
Valvuloplasty: Pretreatment	1 (1.3)	0	0
Valvuloplasty: Posttreatment	0	2 (4.4)	1 (4.2)
Damus-Kayne-Stansel procedure: Pretreatment	0	0	4 (17)
Aortic arch repair: Pretreatment	1 (1.3)	0	0
Aortic arch repair: Posttreatment	1 (1.3)	0	0

Values are presented as n (%). *VSD*, Ventricular septal defect; *RV to PA*, right ventricle to pulmonary artery.

TABLE E2. Coefficient ± standard error (SE) and *P* values for factors associated with time-related survival phases

Factor	Coefficient ± SE	*P* value
Early decreasing phase		
Anatomical (time varying)	1.04 ± 1.5	.5
Physiological (time varying)	2.0 ± 1.6	.2
Late phase (constant risk)		
Anatomical (time varying)	1.7 ± 0.44	.0002
Physiological (time varying)	1.6 ± 0.54	.004

CONG

TABLE E3. Age at operation and 10-year survival, by study

Author (y)	N	Age at operation (y [range])	10-y survival (%)
Gaies and colleagues[16] (2009)	35	2.5 (2.9)	91
Murutza and colleagues[17] (2011)	68	3.2 (25 d-40 y)	83.9
De León and colleagues* (2017)	26	3 (6 mo-18 y)	86†
Lenoir and colleagues[18] (2018)	18	6 (0-37.0)	77
Shin'oka and colleagues[19] (2007)	15	4.6 (3.8)	74.5‡
Hsu and colleagues[20] (2015)	18	8.4 (11.2)	53§

*De Leon LE, Mery CM, Verm RA, Trujiilo-Diaz D, Patro A, Giuzman-Pruneda FA, et al. Mid-term outcomes in patients with congenitally corrected transposition of the great arteries: a single center experience. *J Am Coll Cardiol*. 2017;224:707-15. †Transplant-free survival. ‡15-year survival. §13-year survival.