Biventricular strategies for neonatal critical aortic stenosis: High mortality associated with early reintervention

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Objective: To characterize the risk of reintervention after biventricular strategies to treat neonatal critical aortic stenosis, and the effect of reintervention on survival.

Methods: In a multi-institutional inception cohort of 139 neonates, the time-related risk of reintervention was analyzed using parametric multiphase competing-risk models and a modulated renewal repeated-events method. The risk factors were identified through multivariate regression and selected with bootstrap resampling for reliability. Univentricular survival predictions were generated using the Congenital Heart Surgeons' Society Univentricular Repair Survival Advantage score.

Results: One half of survivors required reintervention within 3 years. The risk of undergoing early reintervention decreased with successive procedures ($P < .0001$); however, second (n = 27) and third (n = 8) reinterventions were associated with a greater late risk of repeat reintervention compared with the index procedure ($P = .02$). The morphologic risk factors for earlier reintervention included left ventricular dysfunction, fewer aortic cusps, associated subaortic or arch obstruction, and a larger tricuspid annulus. The risk of death did not improve after successive reinterventions. Therefore, the overall survival for those requiring repeated reinterventions was compromised by the cumulative procedural risk of death. The most important risk factor for death after the first reintervention ($P < .01$) was a shorter interval from the index biventricular procedure, particularly if less than 30 days. Fifteen neonates required reintervention within 30 days of the index biventricular procedure (9 deaths, 60%). For the same 15 neonates, the survival predictions using published models estimated fewer than one half the number deaths with index univentricular repair strategies (4/15, 27%, $P = .03$).

Conclusions: Success of index biventricular procedures has important survival implications: early reintervention implies a poor prognosis and might reflect incorrect management decisions. The morphologic characteristics can help identify such neonates, and univentricular repair might, instead, be preferable. (J Thorac Cardiovasc Surg 2012;144:409-17)

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Supplemental material is available online.

In neonatal critical aortic stenosis, a decision must frequently be made within the first few days of life between the pursuit of univentricular (1-V) or biventricular (2-V) strategy. This decision is difficult to reverse and can prove fatal if incorrect. The common perception that 2-V physiology is inherently superior to 1-V has led to a clinical bias favoring 2-V strategies.[1]

Several groups have investigated the outcomes after 2-V repair strategies.[2-6] However, despite the occurrence of left ventricular (LV) outflow tract reintervention approaching 50%, the implications of reintervention on survival after 2-V strategies have not been explored.

Therefore, in a multi-institutional inception cohort of neonates with critical aortic stenosis, we investigated the features influencing the time-related risk of reintervention after intended 2-V strategies. Risk factors were sought to help identify patients at elevated risk of reintervention. We then explored the relationship between reintervention and survival. Finally, having identified the high-risk groups, we used the revised Congenital Heart Surgeons' Society (CHSS) critical aortic stenosis prediction model[1,4] to generate the survival estimates had 1-V repair been pursued instead.

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Abbreviations and Acronyms

1-V = univentricular strategy
2-V = biventricular strategy
CHSS = Congenital Heart Surgeons' Society
EFE = endocardial fibroelastosis
LV = left ventricular

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METHODS

From 1994 to 2001, 410 neonates with critical aortic stenosis were prospectively enrolled with the CHSS from 26 member institutions. Critical neonatal aortic stenosis was defined as moderate to severe hemodynamic obstruction to LV ejection and/or a ductal-dependent systemic circulation. Of the 410 enrollees, 366 met the inclusion criteria of atrioventricular and ventricular–arterial concordant connection, patency of the aortic and mitral valves, and aortic arch continuity and underwent intervention within 30 days of life (as a surrogate for the critical nature of the lesion). The initial (index) intervention was the Norwood operation (1-V; n = 223; 61%), 2-V (n = 139; 38%), or cardiac transplantation (n = 4; 1%). Management was at the discretion of the treating physicians. In the present study, we investigated the 139 consecutive infants who underwent an initial (index) procedure indicating an intended 2-V strategy (not including cardiac transplantation). Consent for enrollment and ethics approval were obtained.

Data Acquisition and Analysis

The data were abstracted from institutional medical records regarding patient demographics, preintervention echocardiography and angiography, all procedural details, and autopsy reports in the event of death. Videotape recordings of the echocardiographic examinations were requested from patients whose institutional ethics boards did not preclude their release. These tapes (n = 101) were subsequently examined independently by a blinded examiner to limit interobserver variability. The echocardiographic and morphologic information were otherwise abstracted from the medical reports. A summary of variables used for subsequent multivariate analysis is given in Table E1. The dimensional variables were standardized and are expressed as z-scores on the basis of published normative data[7] if available, or otherwise indexed to either the body surface area or height. Patients' families were contacted annually by the CHSS data center staff.

Endpoints

The endpoints were reintervention and death. Reintervention was defined as any procedure to the LV outflow tract subsequent to the initial (index) intervention, including conversion to Norwood stage I palliation or cardiac transplantation. Death was all-cause mortality after the index intervention.

Parametric multiphase models of time-related transition from the index intervention to mutually exclusive competing endstates (reintervention or death without reintervention) were constructed.[8] (For additional details, see http://www.clevelandclinic.org/heartcenter/hazard.)

Cumulative incidence of reintervention was estimated nonparametrically using the Nelson method.[9] Visual inspection of the risk of each subsequent reintervention revealed a similar temporal pattern. Hence, to investigate the outcomes after successive reinterventions, a form of repeating-events analysis, termed "modulated renewal process method," was used.[10] For this, the patients experiencing a first event were restarted at a new time zero and tracked to the next event, and so forth, for each successive reintervention. The cumulative hazard for all interventions (n = 238) for the 139 patients was then modeled.

Univentricular Survival Predictions

The published CHSS univentricular survival advantage score[1] was used to generate individual time-related survival predictions for the study patients according to their baseline morphology. Aggregated survival predictions were then compared with the actual time-related survival. In addition, the sum of the individual patients' predicted cumulative hazard was used to calculated the expected number of deaths. The expected deaths were then compared with the observed deaths using the chi-square test of 2 proportions.

Statistical Analysis

The data were analyzed using SAS statistical software (SAS Institute, Cary, NC). For time-related parametric models, variable selection was performed by bagging, using baseline (pre-index procedure) demographic, morphologic, and functional indexes. Before each analysis, ordinal and continuous variables were considered by decile analysis to determine possible transformations of scale to improve calibration. Frequency tables were examined, and variables associated with fewer than 5 events were excluded to reduce the risk of overdetermination. Variables with greater than 75% missing values were excluded from the analysis. Missing values were either imputed from normative percentile charts or otherwise imputed with the mean of nonmissing values. A missing value indicator variable was created and tested as a covariate in the regression analysis to verify that the presence of missing data for that factor was not itself a risk factor for the particular event being analyzed. Variable selection (bagging) used 1000 bootstrapped resampled data sets, automated stepwise variable selection, and a P value for retention of .05.[11] The median rule was then applied to individual variables identified in these models and closely clustered variables (eg, various transformations of scale of the same variable).

For analysis of the repeated event reintervention, the sequence of, and interval between, successive reinterventions were added as potential risk factors. The sum of predicted cumulative hazard was compared with the number of observed deaths using the chi-square test. A comparison of the predicted to actual survival was made by visual inspection of nonoverlapping confidence limits.

Presentation

Uncertainty is presented uniformly by ±1 standard deviation, ±1 standard error, or, in the case of proportions or survival estimates, by 68% confidence limits, equivalent to ±1 standard error.

RESULTS

All 139 neonates in the present study underwent an initial index procedure to the LV outflow tract indicating an intended 2-V strategy. During the follow-up period, 64 children underwent a first reintervention, 27 then underwent a second reintervention, and 8 underwent a third reintervention. The nature and sequence of the index procedure and subsequent reinterventions are shown in Figure 1. Balloon aortic valvotomy was the index procedure in 75%, and this strategy was associated with younger age at intervention ($P < .01$), less aortic valve cusp thickening ($P = .02$), and the absence of either a ventricular septal defect ($P < .01$) or important mitral regurgitation ($P < .01$). The decision to pursue balloon valvotomy was independent of the level of obstruction (including subvalvar), LV function, the severity of stenosis, or the grade of endocardial fibroelastosis (EFE).

Time-Related Risk of Reintervention

Risk of reintervention after index procedure for 2-V strategy. After the initial index procedure, infants are

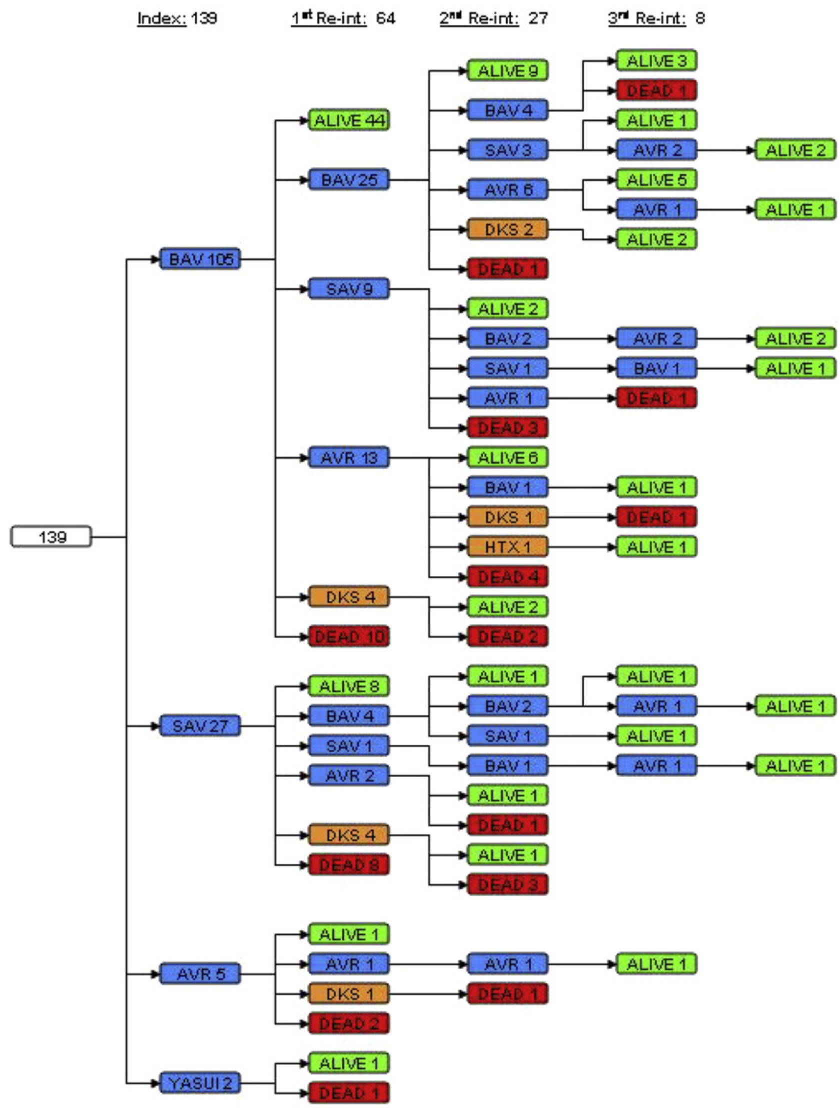

FIGURE 1. Subsequent procedures and mortality for patients who underwent an initial intervention procedure with a biventricular repair strategy intended (n = 139). A total 238 interventions for left ventricular *(LV)* outflow tract stenosis were undertaken in 139 patients. After the index procedure, a first reintervention was undertaken in 64, a second reintervention in 27, and a third reintervention in 8. Of the 238 interventions, 225 were intended biventricular strategy *(2-V)* strategies *(blue)* and 13 represented failure of the 2-V strategy *(orange*; Damus-Kaye-Stanzel anastomosis as a part of a Norwood procedure *[DKS]* in 12 and heart transplantation *[HTX]* in 1). A total 39 children died during follow-up *(red)*; therefore, 100 remained alive *(green)*. Aortic valve replacement *(AVR)* in the study cohort was undertaken with either a Ross-Konno operation or a homograft AVR. *BAV*, Balloon aortic valvuloplasty; *Re-int*, reintervention; *SAV*, surgical aortic valvuloplasty; *YASUI*, Yasui repair (Damus-Kaye-Stanzel and Rastelli operation).

exposed to the mutually exclusive competing risks of reintervention to the LV outflow tract and death without reintervention. Should neither of these events occur, the child remains alive without reintervention (definitively treated at that point in follow-up).

The index 2-V procedure was associated with the risk of early death, and approximately 15% ± 3% died without undergoing reintervention. These children might represent an important group in whom either rapid clinical deterioration preempted reintervention or otherwise reintervention was not possible or deferred.

For infants who survived the index procedure, the likelihood of reintervention was high: 50% within 3 years. The risk was predominantly early; more than 90% of reinterventions occurred within 2 years. The magnitude of the early hazard for reintervention was such that 10 years after the diagnosis, fewer than 40% of the cohort remained definitively treated by a single index procedure. No increasing late-phase hazard for reintervention was observed (to a median follow-up of 8.3 years for the survivors).

Definitive treatment by index procedure. The likelihood of a child being definitively treated by the 2-V strategy

TABLE 1. Incremental risk factors for time-related risk of reintervention to left ventricular outflow tract in neonates with critical aortic stenosis in whom biventricular strategies were pursued

	Modulated renewal (incorporating all interventions)				Index intervention only			
	Risk factor	PE	*P* value	Reliability (%)	Risk factor	PE	*P* value	Reliability (%)
Early phase	Intercept	2.0	.0007	—	Intercept	0.86	.06	—
	Higher operative sequence	1.3	<.0001	99	—	—	—	—
	Fewer aortic cusps*	0.27	.0007	56	Fewer aortic cusps*	0.25	.0017	62
	LV dysfunction	1.1	.0009	50	LV dysfunction	1.1	.0005	87
	Larger TV annulus	0.33	.0008	75	Larger TV annulus	0.36	.0003	83
	—	—	—	—	Presence of subaortic obstruction	1.2	.0295	67
Constant phase	Intercept	–5.2	<.0001	—	—	—	—	—
	Previous intervention	1.4	.0243	66	—	—	—	—
	Higher grade of arch obstruction	0.91	.0106	70	—	—	—	—

Modulated renewal analysis explored risk factors common to successive interventions by analyzing the cumulative hazard from all procedures. In addition, each separate intervention was subjected to risk-hazard analysis to identify risks specific to each sequential intervention. No independent risks were identified for the first and second reinterventions after the index procedure. Reliability was determined by bootstrap resampling (n = 1000). *PE*, Parameter estimate. *Entered as the mean transformation to improve linearity.

index procedure was dependent on the presence or absence of the risk factors for all competing endstates.

The incremental risk factors for reintervention after the index procedure included the presence at diagnosis of LV dysfunction (including mild), fewer aortic valve cusps, the presence of subaortic obstruction, and a larger indexed tricuspid annulus (Table 1). The presence of subaortic obstruction conferred a particularly strong time-related risk of reintervention after the index procedure (>80% risk of reintervention within 1 year). The median tricuspid annular z-score for the study cohort was small (–2.0; range, –6.3 to +1.4). Its influence on the risk of reintervention was therefore not obvious, because tricuspid valves approaching normal dimensions seemingly carry the greatest risk. Larger tricuspid annular z-scores nevertheless correlated with greater grade of regurgitation ($P \leq .004$; parameter estimate, 0.31), smaller LV outflow tract dimensions ($P = .004$, $r = 0.19$), and worse ejection fraction ($P \leq .001$, $r = 0.28$). The risk of reintervention was independent of the type of index procedure (balloon aortic valvotomy in 105, surgical valvuloplasty in 27, Ross-Konno in 5, and Yasui repair in 2) and the age at which it was performed.

At the diagnosis, the incremental risk factors for death (without reintervention) after the index procedure included a greater grade of EFE, the presence of LV dysfunction, and increasing aortic valve cusp thickness (Table 2). The relationship between EFE and survival was exponential. Consequently, severe EFE conferred an especially detrimental effect on survival in infants with critical aortic stenosis in whom a 2-V strategy was pursued (10% ± 18% 5-year survival).

Therefore, in the most favorable circumstances, the likelihood of the index procedure offering definitive treatment is approximately 85% at 10 years for a child with normal LV function, no EFE, a mildly thickened trileaflet aortic valve, and no subvalvar obstruction (Figure 2, *A*). In

TABLE 2. Incremental risk factors for time-related risk of death before subsequent intervention to left ventricular outflow tract (competing risks concept) in neonates with critical aortic stenosis in whom biventricular strategies were pursued

Modulated renewal (incorporating all interventions)				Index procedure				First reintervention			
Risk factor	PE	*P* value	Reliability (%)	Risk factor	PE	*P* value	Reliability (%)	Risk factor	PE	*P* value	Reliability (%)
Intercept	–1.3	.1324	—	Intercept	–3.4	<.0001	—	Intercept	0.45	.1792	—
Greater grade of EFE*	0.10	.0037	78	Greater grade of EFE*	0.11	<.0005	71	Interval to reintervention†	.27	.0032	84
LV dysfunction‡	1.1	.0098	51	LV dysfunction‡	1.1	.0163	71	Surgical first reintervention§	1.9	.0105	54
Younger age†	1.1	.0154	52	Severe aortic cusp thickening||	0.90	.0334	54	—	—	—	—
Smaller distal arch diameter¶	0.78	.0357	76	—	—	—	—	—	—	—	—

Modulated renewal analysis explored risk factors common to successive interventions by analyzing the cumulative hazard from all procedures. In addition, each separate intervention was subjected to risk-hazard analysis to identify risks specific to each sequential intervention. No independent risks were identified for the second reinterventions after the index procedure. Reliability was determined by bootstrap resampling (n = 1000). *PE*, Parameter estimate. *Exponential transformations to improve linearity. †Logarithmic transformations to improve linearity. ‡Any degree of echocardiographic dysfunction. §Surgical procedure (either surgical valvuloplasty, Ross-Konno, Yasui repair, or stage I Norwood palliation) versus balloon aortic valvotomy. ||Severe echocardiographic aortic cusp thickening versus mild or moderate. ¶Luminal diameter (mm) immediately proximal to left subclavian artery indexed to body surface area.

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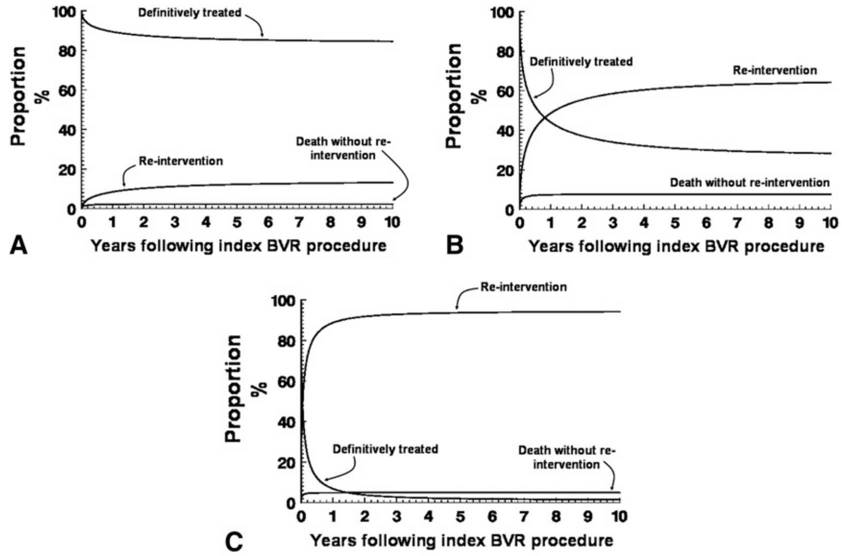


FIGURE 2. Time-related risks of reaching mutually exclusive competing outcomes after biventricular strategy *(2-V)* strategies, stratified according to the presence of A, favorable morphologic features (normal left ventricular *[LV]* function, no endocardial fibroelastosis, no subvalvar obstruction, and a minimally thickened trileaflet aortic valve); B, moderately unfavorable morphologic features (mild LV dysfunction, mild endocardial fibroelastosis, minimally thickened bileaflet valve with no subaortic obstruction); C, unfavorable morphologic features (mild LV dysfunction, moderate endocardial fibroelastosis, a prominently thickened bileaflet valve and the presence of subvalvar obstruction. *Lines* represent parametric determination of the continuous point estimates of the percentage of patients within each category. *BVR*, Biventricular repair.

contrast, in the presence of mild LV dysfunction, mild EFE, and a moderately thickened bicuspid valve, fewer than 30% remain definitively treated by the index intervention 10 years after the diagnosis (Figure 2, *B*). Also, the additional presence of subaortic obstruction reduces the likelihood of the index procedure offering definitive treatment to less than 5% even at 2 years after the diagnosis (Figure 2, *C*).

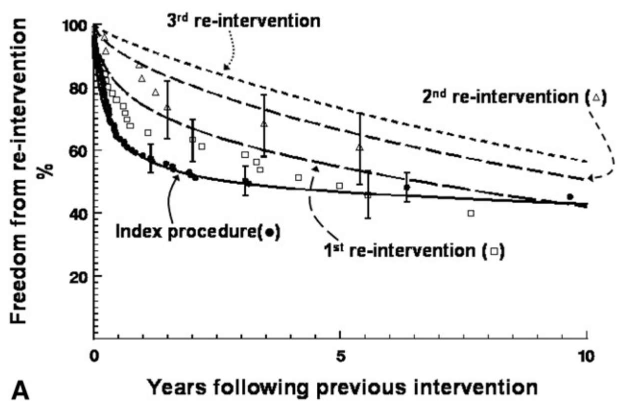
Risk of reintervention from successive procedures. The index intervention was associated with a large early—but continually declining—hazard. By contrast, the second and third reinterventions were associated with progressively decreasing early hazard profiles for reintervention ($P < .001$; Figure 3, *A*). Importantly, however, the second and third reinterventions were also associated with a persisting constant risk of reintervention ($P = .02$; Figure 3, *B*). The constant hazard phase for additional reintervention became predominant approximately 3.5 years after a procedure. The cause for the elevated constant hazard after reinterventions is unclear. However, its presence suggests that despite improved early procedural success, reinterventions are less likely to offer definitive treatment in the long term compared with the index procedure; thus, additional procedures should instead be anticipated.

Effects of Reintervention on Survival

Effect of successive reinterventions on survival. The risk factors for death common to all reinterventions to the LV outflow tract included a greater grade of EFE, the presence of LV dysfunction, younger operative age, and a smaller distal aortic arch (Table 2). In contrast to the hazard profiles for reintervention, successive procedures to the LV outflow tract each exhibited similar early mortality. However, because the risk of death with each intervention was cumulative, an increasing number of reinterventions were associated with an overall greater risk of death.

The profile of risk factors for death after the first reintervention differed from those of the index procedure (Table 2). The influence of the morphologic variables was overshadowed by the nature of the reintervention and the timing of this procedure. Surgical procedures carried significantly greater early hazard for death compared with transcatheter procedures. However, the most important determinant of survival after the first reintervention was a short interval between the index procedure and the first reintervention (Table 2).

Interval to first reintervention: survival implications. A shorter interval between index procedure and the first reintervention (earlier reintervention) was associated with significantly worse subsequent survival. The relationship between the interval and survival was nonlinear, and shorter intervals conferred disproportionately detrimental survival implications (Figure 4, *A*). A threshold of approximately 30 days was apparent (Figure 4, *B*): reinterventions within 30 days of the index procedure offered particularly unfavorable outcomes. If reintervention was necessary within 2 days of the index procedure, the predicted 5-year survival was only 47% ± 10%. By contrast, if reintervention was necessary at 2 months, the predicted 5-year survival was



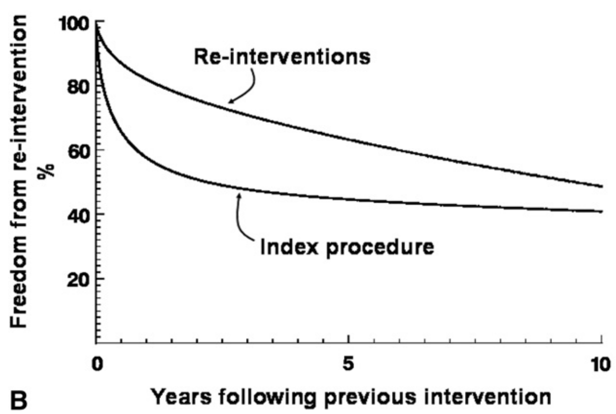


FIGURE 3. A, Modulated renewal analysis of freedom from reintervention after interventions to the LV outflow tract. The parametric model of cumulative hazard for the risk of reintervention for each procedure to the next has been stratified by the sequence of intervention. An increasing sequence of intervention was associated with a progressively declining early hazard for reintervention ($P < .0001$). However, first, second, and third reinterventions were associated with a significantly greater persisting constant hazard for reintervention ($P = .02$). Of the 99 reinterventions, 84 occurred during the early hazard phase and 15 during the constant hazard phase. The constant hazard phase became predominant ≈3.5 years after intervention. B, A stratified plot illustrating the different profile of time-related risk for reintervention between the index procedure and subsequent reinterventions. *Lines* represent parametric determination of continuous point estimates, *symbols* represent Kaplan-Meier estimates at each event (reintervention), *bars* enclose 70% confidence intervals.

76% ± 4%. Therefore, for neonates born with critical aortic stenosis in whom a 2-V strategy is pursued, the success of the initial index procedure has important implications for long-term survival.

Early Reinterventions: Predicted Survival With 1-V Repair

In our study cohort of neonates managed using a 2-V strategy, reintervention within 30 days of the index procedure was necessary in 15 subjects. The clinical indications precipitating reintervention included iatrogenic aortic regurgitation after balloon aortic valvotomy (n = 6), inadequate LV function as evidenced by a low cardiac output state (n = 5), technical failure (n = 2; aortic rupture, wire injury causing acute myocardial infarction), residual stenosis (n = 1), or lethal ventricular arrhythmia requiring open conversion of a transcatheter approach (n = 1; Table 3).

The need for early reintervention might reflect an error at the decision for the initial management. For all infants in whom a 2-V strategy is being considered, 1-V repair is also a feasible alternative management option. In the 15 patients who underwent reintervention within 30 days of their index 2-V strategy, 9 died (60%). For the same 15 children, the CHSS survival model[1] predicted significantly better survival (4/15 deaths) if 1-V repair had been pursued instead ($P = .03$; Figure 4, *C*).

DISCUSSION

Our investigation has indicated that for neonates with critical aortic stenosis in whom 2-V strategies are pursued, survival is strongly associated with the success of the initial index intervention. Therefore, initiatives that optimize the initial decision–management paradigm between 2-V and 1-V strategies might offer important survival benefits. Index procedural failure resulting in early reintervention is associated with particularly high mortality. Children at high risk of early reintervention (procedural failure) include those with LV dysfunction, fewer aortic valve cusps, the presence of subvalvar obstruction, and larger tricuspid annular dimensions. In addition, a number of children with more severe EFE, aortic cusp thickening, and LV dysfunction are at risk of early death. Attempts at 2-V repair through ‘‘trial’’ interventions in the presence of these risk factors could therefore be associated with significant risk. Such children might be better served by an early decision to commit to a 1-V strategy.

That even mild LV dysfunction was associated with an early need for reintervention and death[1,12] is particularly relevant because it implies that ‘‘trial’’ pursuit of a 2-V procedure (eg, balloon valvotomy) in these circumstances is a high-risk strategy.

Both we,[1,4] and others,[13-15] have identified EFE as a particularly strong risk factor for poor survival after pursuit of a 2-V strategy. In addition, the association between aortic valve morphology and outcomes has been noted by others and emphasizes the importance of incorporating these details (as opposed to merely LV dimensions) in the initial decision-making process.[12,16,17]

It is interesting that in contrast to others,[18] we did not identify indexed dimensions of the LV outflow tract to be reliable predictors of reintervention. The reasons for this might relate to the all-inclusive morphologic spectrum of our inception cohort versus the isolated valvar stenosis of other studies.[17] We found that features other than the severity of aortic valve stenosis were the more important determinants.

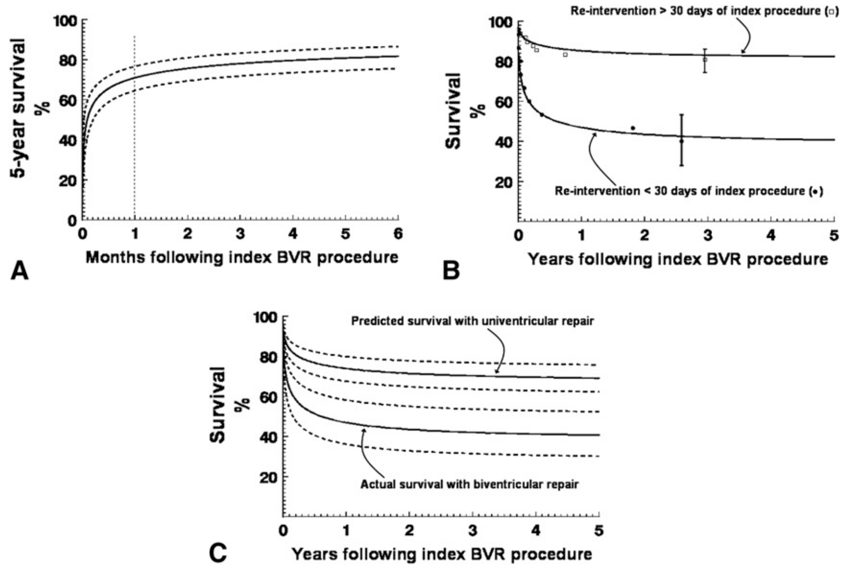


FIGURE 4. A, Nomogram demonstrating 5-year risk-adjusted survival estimates across the range of intervals between the index procedure and first reintervention to the left ventricular *(LV)* outflow tract. Shorter intervals to a first reintervention were associated with disproportionately detrimental survival. Reinterventions within 30 days of the index procedure conferred an especially poor prognosis. *Solid line* represents parametric determination of continuous point estimates, *dashed lines* enclose 70% confidence intervals. B, Survival for the 64 infants who underwent a first reintervention stratified by whether the reintervention was within 30 days of the index procedure or performed after an interval longer than 30 days. Reintervention within 30 days of the index procedure was associated with 41% ± 10% 5-year survival. Reintervention more than 30 days after the index procedure was associated with 82% ± 5% 5-year survival. *Lines* represent risk-adjusted parametric determination of continuous point estimates, *symbols* represent Kaplan-Meier estimates of events (reinterventions), *bars* enclose 70% confidence intervals. C, Observed survival with biventriucular strategy versus expected survival with univentricular palliation for those 15 infants who underwent reintervention to the LV outflow tract within 30 days of the index procedure. Parametric determination of observed survival was 41% ± 10% at 5 years with biventricular strategy. Parametric predictions of expected survival for the same 15 patients was 70% ± 4% with an initial procedure indicating intended univentricular palliation (Norwood stage I operation; $P = .03$). *Solid lines* represent parametric determination of continuous point estimates, *dashed lines* enclose 70% confidence intervals.

Within the duration of follow-up, the absence of a late-phase hazard for reintervention after the index procedure suggested that a group of children exist for whom the initial treatment could be definitive. Identifying these neonates from the outset would be of considerable clinical interest, and our analysis suggests that they might be neonates with normal LV function, minimally thickened trileaflet aortic valves, and no EFE. These features were associated with low mortality and 85% remained free from reintervention at 10 years. By contrast, even mild LV dysfunction, mild EFE, and moderate aortic valve thickening dramatically reduced the chances of definitive treatment. The presence of subaortic obstruction greatly exacerbated these risk factors, and, in this scenario, reintervention was almost universally necessary within 1 or 2 years.

In the present series, the use of transcatheter balloon valvotomy was independent of the level of obstruction, including subvalvar stenosis. For those patients requiring reintervention within 30 days of balloon valvotomy, the indication was residual stenosis in only 10% and severe aortic regurgitation or iatrogenic injury in as many as 90%. It is important to note that Norwood palliation is made considerably more difficult in the face of severe iatrogenic aortic regurgitation. Improving patient selection according to the morphologic features we have identified could offer improved rates of reintervention and survival for infants selected for 2-V strategies. It is possible that the application of balloon valvotomy could presently be less discriminate in today's practice than observed within our study cohort: the initial biventricular repair was balloon valvotomy in 75% of cases, almost certainly under-representative compared with contemporary practice.[13]

That reintervention might be anticipated (or even planned for) mandates an understanding of the effect of reintervention on survival. Successive reinterventions were associated with no lesser procedural risk of early death. Therefore, overall patient survival is a function of the cumulative mortality associated with the number of reinterventions. Consequently, for neonates with critical aortic stenosis, initial decision-management strategies should include an estimation of the long-term risks of reinterventions with consideration to the resulting cumulative mortality.

We recognize several limitations inherent to our analysis. First, the present series was from the late 1990s, with its strength of reliable 10-year follow-up data; however, it is possible that improved application—or technical

TABLE 3. Indications for reintervention within 30 days of index procedure indicating intention to pursue biventricular strategy

Pt. no.	Age (d)	Index procedure	Second procedure	Third procedure	Interval (d)	Indication for reintervention	Died
1	2	BAV	SAV	—	<1	VT and cardiac arrest during BAV	No
2	3	BAV	SAV	—	<1	Aortic rupture and acute tamponade	Yes
3	6	BAV	BAV	Norwood	<1	Wire injury caused myocardial infarction and shock	No
4	23	BAV	Ross	—	<1	Severe aortic regurgitation	Yes
5	1	BAV	Norwood	—	1	Severe aortic regurgitation	No
6	1	BAV	Ross	—	2	Severe aortic regurgitation	Yes
7	7	BAV	BAV	Norwood	8	Severe aortic regurgitation	No
8	2	BAV	Norwood	—	23	Severe aortic regurgitation	Yes
9	4	BAV	Ross	—	8	Severe aortic regurgitation	Yes
10	2	BAV	BAV	Norwood	2	Residual stenosis with duct-dependent circulation	No
11	2	SAV	Norwood	—	<1	Low cardiac output state	Yes
12	3	SAV	Norwood	—	<1	Low cardiac output state	Yes
13	3	SAV	Norwood	—	14	Low cardiac output state	Yes
14	28	SAV	Norwood	—	17	Low cardiac output state	No
15	4	Ross	Norwood	—	<1	Low cardiac output state	Yes

Pt. no., Patient number; *BAV*, balloon aortic valvotomy; *SAV*, surgical aortic valvuloplasty.

refinement—of balloon valvotomy in the intervening period has addressed some of the iatrogenic complications, including reintervention and survival. However, balloon valvotomy has almost ubiquitously replaced surgical valvuloplasty as a first-line treatment of uncomplicated congenital aortic stenosis.[19] Its application might, therefore, be less discriminate than previously, and might translate into high rates of reintervention. In addition, balloon valvotomy has also replaced closed transventricular aortic valvotomy, which some centers had continued to prefer until only recently,[14] despite excellent freedom from reintervention even in complex cases of neonatal aortic stenosis. Second, the present analysis focused only on reintervention and survival. Attention is increasingly shifting toward understanding the long-term functional status of repair strategies, which was not addressed. Third, the present study did not compare the outcomes for 2-V strategies with those of either intrauterine intervention or cardiac transplantation. Additionally, further modifications to 2-V strategies might alter the risk/benefit ratio of such procedures and therefore influence the decision-management paradigm accordingly. Finally, in the present study, we investigated the effect of reintervention to the LV outflow tract. We did not explore the morbidity associated with reinterventions to other left-sided structures, such as the mitral valve. The morbidity resulting from these additional interventions could additionally favor univentricular repair strategies in some children.

In conclusion, for neonates with critical aortic stenosis treated with 2-V strategies, overall survival appears heavily dependent on the success of the initial index intervention. The strong clinical bias toward pursuing 2-V strategies[4] may greatly compromise index procedural success in certain neonates. In particular, earlier reintervention—especially within 30 days of the index procedure—is a strong risk factor for death. Neonates with moderate or severe EFE, LV dysfunction, severe aortic valve cusp thickening, functionally monocusp valves, and subvalvar obstruction are at particularly high risk of death or early reintervention (with subsequent poor survival). Children with these risk factors might be better served by an early commitment to 1-V repair.

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TABLE E1. Selected patient characteristics (preintervention) used for multivariate analysis

Characteristic	Biventricular			
	n	Dead	m	Mean
Dead	139	39	0	39
General				
BSA (m^2)	139	—	0	0.225 (0.12–0.33)
Weight (kg)	139	—	0	3.4 (1.3–6.1)
Age at intervention (d)	139	—	0	6.7 (0–30)
Associated lesions				
Identifiable genetic syndrome	139	0	0	1
Noncardiovascular abnormality	139	3	0	6
Associated cardiovascular abnormality	139	2	0	6
Coarctation	129	7	10	17
Left SVC	139	1	0	1
Anomalous RSCA	139	0	0	2
Septum/endocardium				
ASD	108	10	31	24
VSD	117	4	22	8
EFE grade	96		43	
None		7		48
Mild		11		39
Moderate		3		6
Severe		3		3
LV function/size				
Grade of LV dysfunction	124		15	
Normal		6		53
Mild		4		11
Moderate		9		23
Severe		15		37
Grade of LV hypoplasia	94		44	
Normal		19		74
Mild		6		15
Moderate		2		4
Severe		1		2
Ejection fraction (%)	50	—	89	47 (4–90)
Rhodes score	86	—	53	–0.4 (–4.2–1.9)
Mitral valve				
Parachute MV	101	2	38	3
Mitral regurgitation (moderate or severe)	122	9	17	20
Mitral stenosis (moderate or severe)	115	18	24	35
Z-score MV annulus	108	—	31	–1.4 (–7.0–5.1)
Tricuspid valve				
Tricuspid regurgitation (moderate or severe)	93	5	46	8
Z-score of TV annulus	77	—	62	–2.0 (–6.5–1.8)
AoV structure				
Number of AoV cusps	124		15	
1		5		19
2		22		91
3		3		14
Grade of cusp thickening	75		64	
None		—		0
Mild		10		44
Prominent		15		31
LV outflow tract				
Z-score of AoV annulus	130	—	9	–3.9 (–10.9–1.4)
Z-score at sinuses	91	—	48	–2.9 (–11.7–1.7)
Z-score at sinotubular junction	87	—	52	–0.6 (–5.0–5.2)
Peak LVOT gradient	110	—	29	67 (4–174)

Data presented as mean, with ranges in parentheses. *n*, Number of nonmissing values; *m*, number of missing values; *BSA*, body surface area; *SVC*, superior vena cava; *RSCA*, right subclavian artery; *ASD*, atrioseptal defect; *VSD*, ventriculoseptal defect; *EFE*, endocardial fibroelastosis; *LV*, left ventricular; *MV*, mitral valve; *TV*, tricuspid valve; *AoV*, aortic valve; *LVOT*, left ventricular outflow tract.

CHD