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Critical left ventricular outflow tract obstruction: The disproportionate impact of biventricular repair in borderline cases

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Objective: In critical left ventricular outflow tract obstruction, the common perception that biventricular physiology is superior to univentricular physiology has led to a bias favoring biventricular repair. We hypothesized that pursuit of biventricular repair in borderline candidates increases mortality.

Methods: Between 1994 and 2001, 362 neonates with critical left ventricular outflow tract obstruction were prospectively enrolled by 26 institutions. Initial procedure indicated intended univentricular repair (n = 223; 84 deaths) or biventricular repair (n = 139; 39 deaths). Parametric risk–hazard analysis identified predictors of death for univentricular and for biventricular repair, which allowed prediction of the 5-year univentricular survival advantage for every infant. Survival was scrutinized for children managed discordantly to univentricular survival advantage predictions.

Results: Incremental factors for death after univentricular repair were as follows: tricuspid regurgitation, smaller mitral annulus z-score, smaller indexed dominant ventricular length, and presence of a large ventricular septal defect; risk factors after biventricular repair were as follows: minimum left ventricular outflow tract diameter, endocardial fibroelastosis, left ventricular dysfunction, and smaller mid-aortic arch. These variables formed the univentricular survival advantage tool (all $P < .0001$, $R^2 = 0.92$). Discordant management was more common with biventricular than with univentricular repair (56% vs 21%; $P < .01$). Discordant pursuit of biventricular repair was associated with significantly more observed versus expected deaths (biventricular repair 30 vs 14; $P < .001$; univentricular repair 20 vs 13; $P = .02$). Survival after biventricular repair is sensitive to changes in univentricular survival advantage values, especially in borderline candidates. In contrast, univentricular repair survival is insensitive to changes in univentricular survival advantage values.

Conclusions: Inappropriate pursuit of biventricular repair in borderline candidates is more frequent and more consequential in survival terms than is inappropriate pursuit of univentricular repair. Use of the univentricular survival advantage tool will help identify infants for whom univentricular repair may be a better choice than attempting biventricular repair.

In treating the spectrum of critical left ventricular outflow tract (LVOT) obstruction, making the wrong initial choice between biventricular (BVR) versus univentricular repair (UVR) can prove fatal. The common perception that biventricular physiology is inherently superior to univentricular physiology has led to a bias favoring BVR.[1] We hypothesized that pursuit of BVR in borderline candidates increases mortality.

The Congenital Heart Surgeons' Society (CHSS) has previously published a prediction model to aid in optimal decision-making for neonates with critical LVOT obstruction.[1] We subsequently discovered that the decision logic was overly sensi-

Abbreviations and Acronyms

BAV = balloon aortic valvotomy
BVR = biventricular repair
CHSS = Congenital Heart Surgeons' Society
EFE = endocardial fibroelastosis
LVOT = left ventricular outflow tract
UVR = univentricular repair
UVR-SA = univentricular repair survival advantage
VSD = ventricular septal defect

tive to age at admission. In addition, the increasing occurrence of antenatal diagnosis complicates the determination of precise age at admission. Therefore, we have refined the model by expanding the cohort, extending follow-up duration, and using more robust analytic methods. Using the new model, we categorized actual management strategies as concordant or discordant with respect to the model's prediction for optimal survival. The survival impact of discordant decisions was evaluated.

Patients and Methods

Between 1994 and 2001, an inception cohort of 410 consecutive neonates with a diagnosis of critical LVOT obstruction was prospectively recruited by 26 CHSS institutions. Choice of treatment strategy was at the discretion of the treating physicians. Participation in this project and submission of patient information were voluntary and confidential. Both parental consent for enrollment and ethics board approval were obtained by individual institutions and the CHSS Data Center.

Critical neonatal LVOT obstruction was defined as stenosis occurring at any level from the subvalvular region to the innominate artery with or without left ventricular hypoplasia, such that the systemic circulation was ductus dependent. Of the 410 neonates, 366 met inclusion criteria of atrioventricular and ventriculoarterial concordant connections, aortic and mitral valve patency, and aortic arch continuity and underwent an intervention to relieve obstruction within 30 days of birth. We excluded 4 patients referred for cardiac transplantation from subsequent analysis, leaving a study cohort of 362 neonates (Figure E1).

Patient data were accrued and managed as previously described.[1] Echocardiograms (n = 214 patients) were requested and reviewed by a blinded examiner. If echocardiograms were not available, functional and morphologic indices (Table E1) were extracted from reports. Patients' families were contacted annually by the CHSS Data Center staff, and completeness of this follow-up was 88% in 2006.

Procedures

Intent to treat was determined by the index intervention directed toward the LVOT. UVR was pursued in 223 neonates (62% of the cohort) with stage I Norwood palliation (Figure E2). Of these, 6 underwent transplantation, and 1 was converted to BVR. All are included in the UVR analysis.

BVR was pursued in 139 neonates (38% of the cohort). Index intervention was balloon aortic valvotomy (BAV) (n = 105), surgical aortic valvuloplasty (n = 34), autograft aortic valve replacement (Ross–Konno procedure,[2] n = 5), and Yasui procedure[3,4] (n = 2) (Figures E3 and E4). Of these, 1 underwent transplantation and 11 were converted to UVR. All are included in the BVR analysis.

Analytic Methods

The analytic objective was to determine the 5-year survival advantage conferred by pursuing UVR versus BVR. We refer to this calculated UVR survival advantage as the UVR-SA decision tool.

UVR-SA decision tool. Development of the UVR-SA tool included the following: (1) separate risk factor analyses for death after intended UVR and BVR management, (2) prediction of 5-year survival for each patient with either strategy using these analyses, and (3) identification of predictors for the survival difference between strategies.

Separate parametric models for time-related survival after intended UVR and BVR were generated as previously described.[1,5] However, covariates representing age or surrogates thereof were suppressed in the current multivariable analyses (see below). One new covariate investigated was minimal LVOT diameter (regardless of level). Variable selection used bagging.[6] One thousand bootstrap samples were analyzed automatically with $P = .1$ for retention of variables. Those appearing in 50% or more of bootstrap models or clusters were considered reliable for inclusion in the final models.

Age at admission and age at first intervention were suppressed in both UVR and BVR models. We tested this decision by exploring correlation of age with morphologic and functional variables, its colinearity with other variables and survival, goodness of fit of the model with and without age, and its relation to decision management.

Using the UVR and BVR multivariable equations, we estimated 5-year survival for each patient, first as if the patient had undergone UVR and second as if the patient had undergone BVR. Differences between predictions for UVR 5-year survival and BVR 5-year survival were analyzed by bagging and linear regression to generate the UVR-SA tool.

Use of UVR-SA tool to classify discordant management decisions. For each patient, the UVR-SA values were calculated and used to predict the "optimal management decision" for that patient.

A positive value favors UVR management and a negative value favors BVR management. For a given patient, if predicted 5-year survival for UVR is 75% and for BVR is 60%, the UVR-SA value would be +15, indicating a 15-point survival difference favoring UVR. Alternatively, if predicted survival for UVR is 52% and for BVR is 60%, the UVR-SA value would be −8, indicating an 8-point survival difference favoring BVR. A UVR-SA value of zero indicates that predicted survival is equal with either approach, and therefore neither is favored over the other.

When the UVR-SA prediction was in accordance with clinical intent to treat, management was labeled as "concordant." When the UVR-SA prediction was not in accordance with clinical intent to treat, management was labeled as "discordant."

Survival consequences of discordant management. Three methods were used to compare actual survival with best predicted 5-year survival according to the UVR-SA value. For each group

(UVR concordant, UVR discordant, BVR concordant, BVR discordant), Kaplan–Meier survival estimates were generated. In addition, for each patient, cumulative hazard was estimated at the time of follow-up by the multivariable equation for the management pathway associated with the best predicted 5-year survival. Expected number of deaths was the sum of these cumulative hazard estimates. This was compared with actual deaths by the χ^2 test. Finally, for each patient a survival curve was generated by the multivariable equation for the management pathway with the best predicted 5-year survival. Survival curves for infants within each of the 4 groups were aggregated and the mean was compared with corresponding Kaplan–Meier estimates.

Results

Elements of the UVR-SA Tool

Risk factors for death differed by management strategy (UVR vs BVR).

Five-year unadjusted survival after UVR was 62% ± 3% (Figure E5). Incremental risk factors for death included moderate or severe tricuspid regurgitation ($P < .01$), large ventricular septal defect (VSD, $P = .01$), smaller mitral valve z-score ($P < .01$), and smaller indexed length of the dominant (apex-forming) ventricle ($P = .02$). Moderate or severe tricuspid regurgitation or a large VSD were associated with especially poor survival (Figure E6).

Five-year unadjusted survival after BVR was 71% ± 4% (Figure E5). Incremental risk factors for death included smaller minimum indexed LVOT diameter ($P < .01$), left ventricular dysfunction ($P = .02$), higher grade of endocardial fibroelastosis (EFE, $P < .01$), and smaller indexed mid-aortic arch diameter ($P = .05$). Severe EFE or LVOT diameters smaller than 4 mm were associated with especially poor survival after BVR (Figure E7, *a*).

The regression equation for 5-year survival advantage of UVR over BVR (UVR-SA tool) included the 8 risk factors for death after BVR or UVR (Table 1; $R^2 = 0.92$).

TABLE 1. Incremental risk factors for time-related death for patients who had an initial procedure indicating an intended biventricular repair pathway

Covariate	Estimate	*P* value
Intercept	−.484	<.001
Presence of moderate or severe tricuspid regurgitation	−.279	<.001
Z-score of mitral valve annulus	+.030	<.001
Presence of large VSD	−.312	<.001
Length of apex-forming ventricle (cm)*	+.715	<.001
Minimum diameter of the LVOT (cm)†	+.892	<.001
Presence of left ventricular dysfunction‡	+.230	<.001
Grade of endocardial fibroelastosis§	+.165	<.001
Diameter of the mid-aortic arch (cm)‖	−.187	<.001

Risk factors in normal font represent those identified as predictors for death after univentricular repair and those in italicized font represent those identified as predictors for death after biventricular repair. *VSD,* Ventricular septal defect; *LVOT,* left ventricular outflow tract. *Echocardiographic measurement from crux of the heart to the apex, regardless of whether formed by the left or right ventricle. Indexed to height of the patient. †Minimum diameter measured at any point from the subvalvular region as far distal as the brachiocephalic artery. Indexed to body surface area and entered after inverse transformation. ‡Presence of any degree left ventricular dysfunction, including mild. §Endocardial fibroelastosis was graded subjectively by the echocardiographic appearance of left ventricular endocardial brightness and thickening as follows: 0 = none; 1 = involvement of papillary muscles only; 2 = papillary muscle with some endocardial surface involvement; 3 = extensive endocardial surface involvement. ‖Measured immediately proximal to the left subclavian artery and indexed to the body surface area.

Investigating the Decision to Suppress "Age" Variables

For UVR, older age at intervention was weakly associated with higher mortality but younger age was not. In contrast, for BVR, younger age had a disproportionately strong association with higher mortality (Figure 1, *a*) and discordant decision making (Figure 1, *b*). Very young age at intervention in the BVR group was determined by smaller aortic valve z-score (rather than minimum LVOT diameter at other levels) and not other features (for example left ventricular dysfunction). However the smaller aortic valve z-score was only associated with young age at BVR intervention for those infants discordantly managed (Figure 1, *c*).

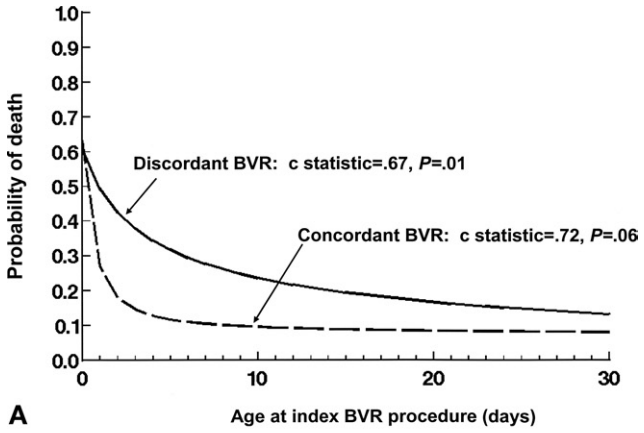
Left ventricular dysfunction and arch hypoplasia were found to be colinear with age in the BVR model; thus, goodness of fit of the model without age (log likelihood = −48.44 and with age in place of these 2 variables (log likelihood = −48.45) were nearly identical. Therefore, left ventricular dysfunction and arch hypoplasia replaced age as covariates within the model, with no loss to overall goodness of fit.

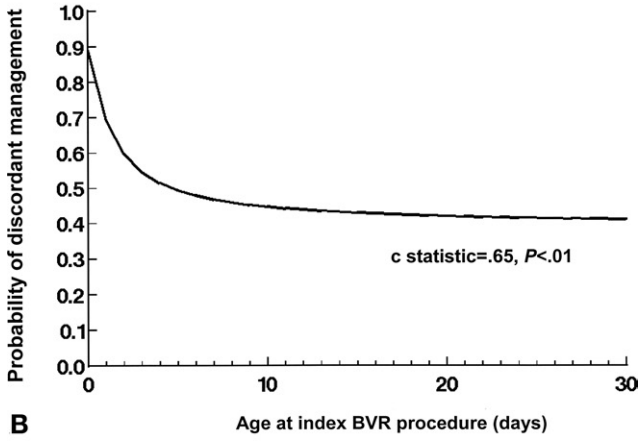
Use of UVR-SA Tool to Classify Discordant Management Decisions

The distribution of UVR-SA values in the 362 study patients ranged from +78 (strongly favoring UVR) to −81 (strongly favoring BVR) with a median of +15. For a neonate with the mean UVR-SA value of +15, predicted 5-year survival is 15% better with UVR than with BVR. UVR-SA value was negative in 30% of patients (favoring BVR) and positive in 70% (favoring UVR).

The median UVR-SA value within the UVR group was +29 (range −81 to +78, Figure 2, *dashed line*). A positive value (79% of this group) indicated that the actual strategy pursued was concordant with the predicted strategy of the UVR-SA value ("UVR concordant"). A negative score (21% of this group) indicated that the strategy pursued was discordant with the predicted strategy ("UVR discordant").

The median UVR-SA value within the BVR group was +4 (range −32 to +78, Figure 2, *solid line*), indicating a 4% survival advantage for UVR. The UVR-SA value was negative in 45% of this group, indicating concordance be-





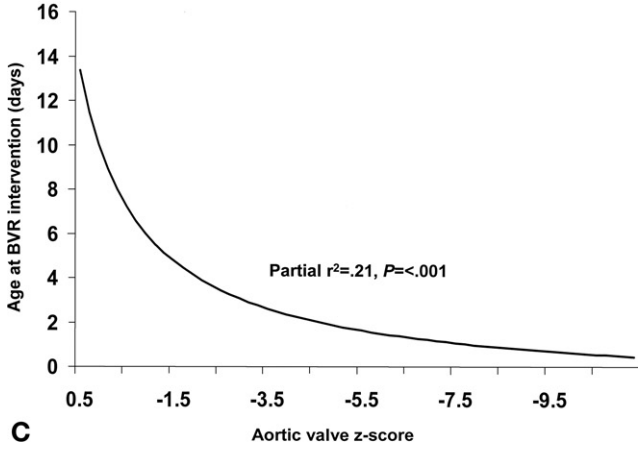


Figure 1. Exploration into the association between age and BVR management. A, The logistic probability of death after intended BVR follows an inverse relationship to the age at index intervention. Discordantly managed patients (*solid line*) carry a higher risk of mortality at all ages, but especially so at young ages. Mortality for concordantly managed patients (*broken line*) is only associated with extremely young ages (<days). B, The probability of receiving a BVR discordant management is strongly associated with young age at intervention. C, The aortic valve z-score is the strongest predictor of age at intervention, but only in the BVR discordant group ($r = 0.45$). For concordant BVR management there is no relationship between aortic valve z-score and age at intervention ($r = 0.06$). Collectively, these findings imply that very early BVR intervention (BAV in 83% younger than 3 days) driven by small aortic valve z-scores is frequently a discordant decision with a high incidence of death. The UVR-SA tool will identify patients in whom UVR would offer better survival in tight valvular aortic stenosis. *BVR*, Biventricular repair; *BAV*, balloon aortic valvotomy; *UVR-SA*, univentricular repair survival advantage.

tween the UVR-SA predictions and the actual strategy pursued ("BVR concordance"). In 55%, however, the UVR-SA value was positive, indicating that predicted survival was better with UVR, and these infants were labeled "BVR discordant."

Survival Consequences of Discordant Management

Five-year survival with UVR management was similar with concordant and discordant management, 63% versus 56%, respectively. If BVR had been pursued for discordant UVR patients, the predicted 5-year survival would have been 70% (Figure 3) and 7 deaths may have been prevented (20 actual vs 13 expected with BVR management; $P = .02$, Table 2).

Five-year survival with concordant BVR management was 85%, and with discordant BVR management, 60%. If UVR had been pursued for discordant BVR patients, the predicted 5-year survival would have been 81% (Figure 4) and 16 deaths may have been prevented (30 actual vs 14 expected with UVR management; $P < .001$, Table 2).

Discordant decisions result in a decrease in survival in both UVR and BVR cohorts. However, a discordant BVR decision is more expensive in survival terms than a discordant UVR decision. This is because BVR survival is highly sensitive across the range of UVR-SA values (Figure 5, *a*), whereas UVR survival is relatively impervious to changes in UVR-SA values (Figure 5, *b*).

Discussion

Principal Findings

UVR-SA tool. Our revised UVR-SA tool is a decision aid that compares predicted survival with UVR and BVR across the full spectrum of critical LVOT obstruction. It incorporates morphologic, functional, and pathologic information to determine the relative risks associated with the pursuit of one strategy versus the other. For any particular child, the relative predominance of risk factors, therefore, determines which strategy is associated with the more favorable survival prediction.

Determinants of survival after UVR. Tricuspid regurgitation is associated with increasing mortality after UVR and was also identified in the previous CHSS prediction model[1] and this revision. It contributes to volume overload,

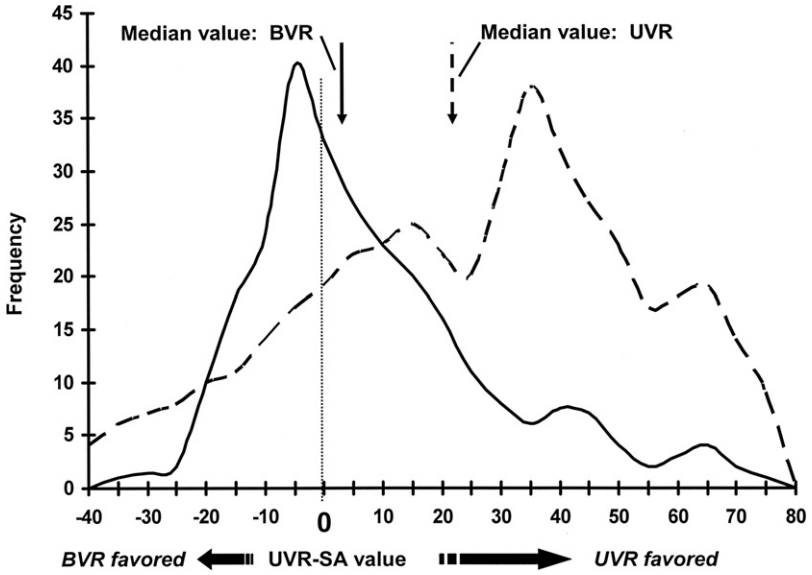


Figure 2. Distribution histogram of UVR-SA values for the BVR (solid line) and UVR *(dashed line)* cohorts. The median value was +29 for the UVR group *(dashed arrow)* and +4 for the BVR group *(solid arrow).* All of those 176 UVR children (79%) with a UVR-SA value > 0 had better predicted survival with UVR and therefore their management was "concordant" with the UVR-SA predictions. The 47 UVR children (21%) with a UVR-SA value < 0 had better predicted survival with BVR and therefore their management was "discordant." All of the 63 BVR children (45%) with a UVR-SA value < 0 had better predicted survival with BVR, and therefore their management was "concordant" with the UVR-SA predictions. Those 76 UVR children (55%) with a UVR-SA value > 0 had better predicted survival with UVR, and therefore their management was "discordant." See Figure 1 for definitions of abbreviations.

right ventricular failure, and compromised cardiac output. Attempts to repair established or new-onset tricuspid regurgitation are increasingly being made to reduce attrition after the Norwood palliation and improve the chances of successful Fontan repair.[7]

Mitral annular size correlates highly with left heart structural dimensions and also with mortality after UVR, and it likely represents a robust surrogate for overall left-sided structural hypoplasia. A small annulus did not correlate with mitral stenosis or regurgitation. Although UVR largely neutralizes the inadequacy of the left ventricle, others have demonstrated improved survival after Norwood palliation in situations in which the left heart is not hypoplastic.[8,9]

Larger indexed length of the dominant ventricle was associated with improved survival in UVR. Because the dominant ventricle was almost exclusively the right ventricle, this variable may reflect the functional adequacy of the right ventricle in assuming the systemic role. Right-sided functional variables were sparse in our UVR-SA model development and those of others.[10,11] The identification of this unusual variable therefore reinforces the need to more closely quantify the influence of right ventricular features on outcome in critical LVOT obstruction.

Although we have found the presence of a large VSD to be associated with increased mortality after UVR, we cannot offer an explanation for this.

Determinants of survival after BVR. Both here and previously,[1,11,12] EFE has been identified as an important predictor of death after BVR, even when left ventricular function is adequate. Although the reliability of diagnosing EFE by echocardiography has been questioned, we[1] have previously demonstrated correlation between preintervention evaluation and findings at autopsy. Furthermore, we and others[11] have found that thickened echobright endocardium is a robust prognostic determinant, regardless of true correlation with pathologic specimens.

A newly considered variable, the minimum LVOT dimension (regardless of level), was a more reliable risk factor than any single level of LVOT obstruction, including the aortic valve. A small aortic valve z-score is, however, a feature associated with early BVR intervention (particularly BAV) and death,[1,11,13] especially in very young children.[1] Inclusion of the broader concept of minimum LVOT dimension allows identification of additional neonates with more

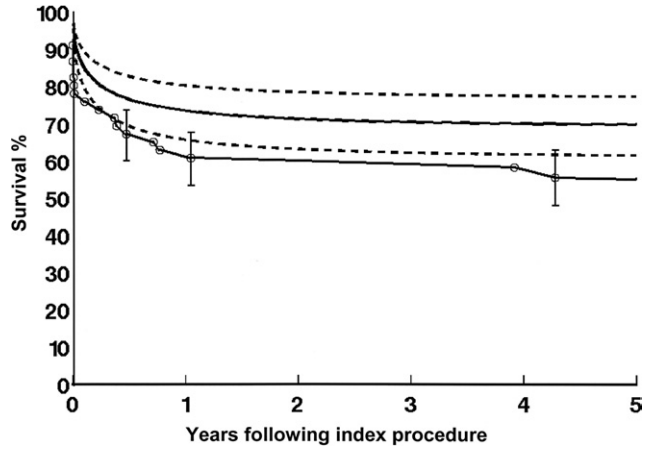


Figure 3. Actuarial Kaplan–Meier survival of UVR infants managed *discordantly (circles),* compared with parametric predicted survival for the same patients if they had instead received BVR as the UVR-SA decision tool advised. *Error bars* and *dashed lines* enclose 70% confidence intervals. Survival differences are significant ($P = .02$). *UVR,* Univentricular repair; *BVR,* biventricular repair; *UVR-SA,* univentricular repair survival advantage.

TABLE 2. Comparison of actual and expected deaths between the study groups

	No. of patients	% Incorrect	Expected deaths	Actual deaths	Predicted vs actual
UVR concordant	177	0	59 (33%)	64 (36%)	.47
BVR concordant	61	0	8 (13%)	9 (15%)	.71
UVR discordant	46	21	13 (28%)	20 (43%)	$P = .02$
BVR discordant	78	56	14 (18%)	30 (38%)	$P < .001$

UVR, Univentricular repair; *BVR,* biventricular repair.

diffuse LVOT hypoplasia who also respond poorly to aortic valvotomy. An indexed LVOT diameter smaller than 16 mm/m^2 (equivalent to 4 mm for a body surface area of 0.25 m^2) confers disproportionately poor predicted survival after BVR (Figure E7, *a*).

The importance of diffuse LVOT hypoplasia is emphasized by the impact of distal arch dimensions on survival after BVR. More diffuse phenotypic disease is likely to be less amenable to either surgical or balloon valvotomy alone. In some infants, distal arch hypoplasia and coarctation may predominate, a condition recently termed hypoplastic left heart complex.[14] This latter circumstance requires intervention directed primarily toward the arch and we therefore consider it a separate entity.

Age. Suppression of age in this revision of the UVR-SA prediction model does not undermine its clinical importance. Other informative variables have instead been incorporated without compromising goodness of fit. Age variables are problematic, first because of imprecision (age at admission) and second because they may be prone to manipulation (age at intervention). Variables that may be manipulated by the user are inherently undesirable for a predictive model based on patient-specific characteristics. For example, no inference can be made that delaying the date of

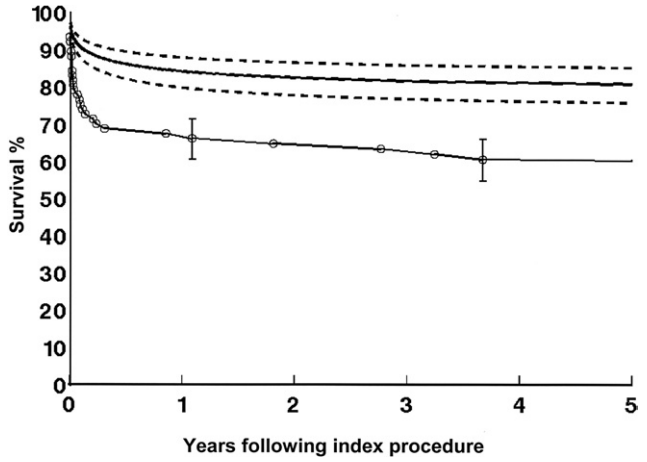


Figure 4. Actuarial time-related survival of biventricular patients managed discordantly (circles), compared with parametric continuous point estimates of survival for the same patients if they had instead received UVR in accordance with UVR-SA tool predictions. *Error bars* and *dashed lines* enclose 70% confidence intervals. Survival differences are significant ($P < .001$). *UVR-SA,* univentricular repair survival advantage.

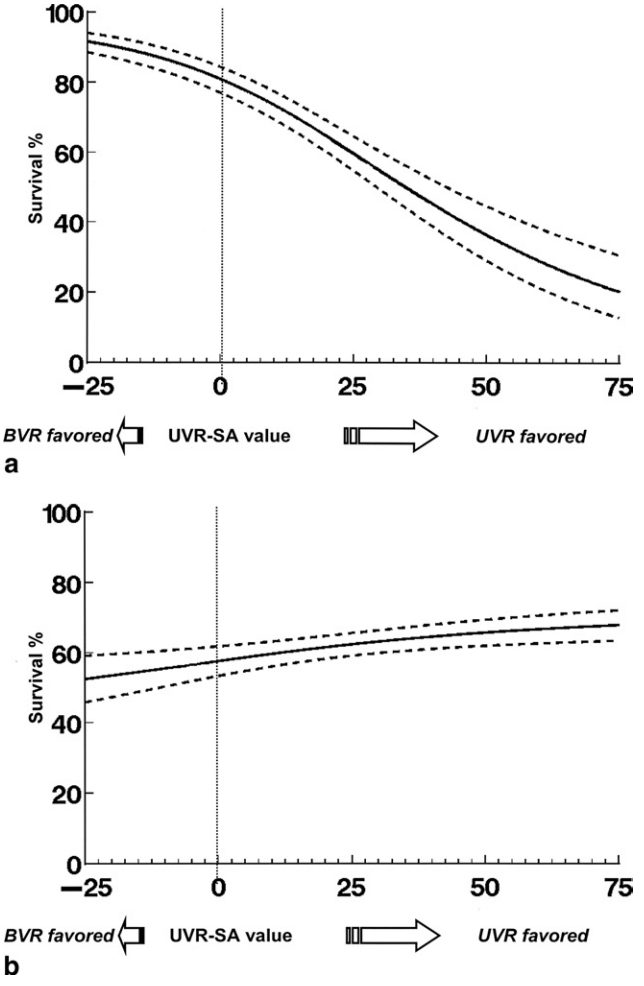


Figure 5. Parametric continuous point estimates of predicted 5-year survival for (a) BVR or (b) UVR across the spectrum of UVR-SA values. The 95th centiles for UVR-SA values in the CHSS critical LVOT obstruction cohort range from −24 to +66. *Fine dashed lines* enclose 70% confidence intervals. Survival for BVR is far more sensitive to changes in UVR-SA values. The steep slope of the BVR curve (a) corresponds to a sharp fall in survival. See Figure 1 for definitions of abbreviations.

intervention will alter outcome, yet the inclusion of age provides the potential for this erroneous decision logic. In addition, the increasing advent of fetal diagnosis further confounds the use of admission age as a variable.[15] Because young age is an especially strong determinant of poor outcome after BVR, small inadvertent variations will result in large predictive differences.

Interestingly, young age is a risk factor for BVR[16] but not for UVR (where it may even be protective.[17]) We therefore explored functional and anatomic features for which young age at BVR is a surrogate. Only a smaller aortic valve z-score was identified, and this was only within those BVR infants discordantly managed (the majority by BAV). The inference is that tight, discrete aortic valve stenosis requiring very early intervention is often managed by BAV, with high resulting mortality. The UVR-SA tool identifies 80% of these high-risk infants as being better served by UVR. The impact of BVR (especially BAV) in extremely young neonates needs to be further explored.

Alternative models for critical LVOT obstruction. Other prediction models have been devised for critical LVOT obstruction, including the Rhodes score,[10] which has been recently tested against the previous CHSS model.[11] However, the Rhodes score was generated in a homogeneous subset of infants with discrete valvular stenosis (not necessarily ductus-dependent), all of whom had BVR. It is therefore applicable only to the most favorable cases, ideally suited to BAV. Furthermore, it provides no survival comparison with an alternative strategy. Colan and associates[11] have nevertheless reported the revalidation of the Rhodes score, although in a population of infants preselected for BVR on the basis of favorable features.

UVR-SA tool to improve decision management. In the clinical arena, we recognize that the UVR-SA tool should be seen as an aid to decision making, not a rule. The UVR-SA tool must be applied to an individual patient in the context of local expertise and family preference. However, larger UVR-SA values should prompt greater caution when pursuing discordant management than more modest (borderline) values. Furthermore, the sensitivity of BVR survival to changes in UVR-SA indicates that discordant pursuit of BVR is more costly in survival terms than discordant pursuit of UVR. In fact, infants receiving discordant BVR display the best predicted UVR survival (80% at 5 years).

Limitations

Several limitations are inherent in the use of our prediction model. Although the tool integrates complex information, it does not include all patient characteristics or factors specific to an individual institution. Also, the UVR-SA tool uses survival as the end point, without considering functional performance, reintervention, or quality of life, which are all important considerations. This present analysis identified only early hazard phases. It is likely that late hazard phases exist for both strategies, particularly after UVR.[18] Similarly, the impact on survival of unplanned reintervention after BVR is not clearly understood.

The use of death as the primary end point has not included "crossovers" to opposite strategies as "events." However, crossover from BVR to UVR (n = 12, 9%) was considerably more frequent than the converse (n = 7, 3%). Therefore, an analytical strategy incorporating crossovers as events further biases against BVR in borderline cases and would strengthen our message further.

As practice evolves with the more widespread use of modalities such as the Ross–Konno procedure, hybrid palliation,[19] and modifications of the Yasui procedure,[4] the UVR-SA will require recalibration with new cohorts and continued follow-up. The CHSS is presently enrolling a contemporary cohort for the purposes of model revalidation and refinement while exploring modern treatment modalities and investigating functional outcomes.

The advantage of studying a multi-institutional cohort is that the full spectrum of management strategies (and outcomes) is incorporated. However, a disadvantage is that institution-specific factors may influence the development and application of a predictive model. For example, institution-specific differences in outcome may have biased the risk factors associated with one strategy or the other. Similarly, the applicability of the model's predictions may be jeopardized by differences in local technical expertise.

Finally, this analysis has been undertaken on a cohort between 1994 and 2001. Although outcomes of all procedures are likely to have improved since then, we would contend that outcomes after UVR have enjoyed a more pronounced relative improvement. For example, several groups are reporting operative mortality below 20%[20] and even approaching 10%[21,22] after stage I Norwood palliation. Relatively greater improvements in UVR survival would further strengthen our conclusions.

Implicit in the use of prediction models is that heeding their advice will translate into improved clinical outcomes. The ideal revalidation of our model would involve a prospective trial in which infants managed in accordance with the UVR-SA tool are compared with infants managed according to current clinical practice. Such a trial seems unlikely. However, a cohort of neonates with LVOT obstruction that the CHSS is presently enrolling will serve as an ideal substrate for comparing the overall predictive accuracy of survival.

Conclusions

The UVR-SA tool identifies morphologic and functional indicators of poor outcome before intended UVR or BVR. The greater the magnitude of the UVR-SA value, the greater the potential survival cost when pursuing a discordant strat-

egy. Discordant pursuit of BVR in borderline candidates is more frequent than the discordant pursuit of UVR, likely driven by an intuitive notion that "two ventricles are better than one." Discordant BVR is more costly in survival terms than discordant UVR. Use of the UVR-SA value will identify infants for whom UVR may be better than attempting BVR in the face of challenging morphologic, functional, and pathologic features. The UVR-SA is freely available on the CHSS Web site (www.chss.org).

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Discussion

Dr Edward L. Bove *(Ann Arbor, Mich).* I would like to thank Dr Hickey and his coauthors from the CHSS for an excellent study with a new, at least to me, statistical evaluation tool. In this presentation, the authors have asked the age-old question: "Is a high-risk BVR better than a low-risk UVR approach?" Despite the substantial decline in early mortality for univentricular approaches, most centers still desire to push borderline patients to a BVR, believing that it is safer and affords better long-term outcome. The authors have documented that the first assumption is not always correct, although the second still remains uncertain. Further complicating this decision process is the realization that, at least for the types of patients in this particular analysis, namely, those with critical LVOT obstruction, the single-ventricle approach perhaps offers the best outcomes among many variants of hypoplastic left heart syndrome.

The authors performed an exhaustive analysis of multiple risk factors for death for both UVR and BVR and then formed a UVR-SA tool that allowed them to reanalyze predicted survival for those whose repair was either concordant or discordant using predictive formulas previously published. This model was further refined and used to predict an optimal survival path for the patients in the analysis.

Although there are multiple intriguing findings among these data, the authors found that discordant decision-making, namely, pursuing BVR when UVR had a higher predicted survival or vice versa, costs lives. More important, a discordant BVR decision is more costly than a UVR one. The inference is that the marginal left heart, for whatever reason, has little or no room to compensate and transfers all the risk up front. Equally important, although not addressed here, is the potential that many BVR survivors may also face repeated valve replacement procedures and pulmonary hypertension in their later years. I have 2 questions for Dr. Hickey.

It seems from the analysis of their paper that a smaller mitral valve annulus was a risk factor only for UVR. Others have reported that the mitral valve size was strongly predictive of outcome for BVR. Could the authors provide some insight regarding the influence of the mitral valve, either size or function, on survival for BVR patients?

Second, do the authors believe that the more liberal use of Ross–Konno procedures, either with or without arch repair as

needed or even resection of EFE, might improve survival for BVR?

I thank Dr. Hickey for an excellent presentation.

Dr. Hickey. Thank you very much, Dr. Bove, for your comments and your questions. The issue with the mitral valve annulus is intriguing, because, as you point out, it was identified as a risk factor for death following univentricular repair, which is clearly a surprise. We explored this further, and our conclusions are as follows.

The mitral annular Z scores as a risk factor for univentricular repair do not correlate with either mitral stenosis or mitral regurgitation in this cohort. Therefore, this variable, although representing the mitral annulus, is not necessarily a functional variable. It is a morphological dimension that correlates strongly with overall left-sided structural hypoplasia. So it correlates with dimensions of the LV outflow tract and the ventricular size and ventricular hypoplasia. So it is in some ways misleading that it is the mitral annulus. It is, we feel, a variable representing the overall dimension and degree of left-sided hypoplasia.

So why is it not a risk factor for biventricular repair? Well, the answer to that is that we obviously looked at and explored the potential for both functional regurgitation or stenosis as a risk factor after biventricular repair, including mitral morphology and dimensions. All of these variables were overshadowed in our statistical analysis by more robust variables—namely, the degree of LV dysfunction—and particularly the severity of endocardial fibroelastosis or thickening, which is an extremely strong predictor of poor prognosis after biventricular repair. So although we don't deny that mitral valve variables have been reported as important in other series, here they have been overshadowed by other functional and morphologic left-sided variables.

In regard to your second question and the use of neonatal Ross–Konno procedures, we have been looking at the *index* procedure as the intention to treat. Invariably in our series this was either through balloon aortic valvotomy or surgical valvotomy, with only a minority of more complex repairs (namely, 2 Yasui and 5 index Ross–Konno procedures). A number of other Ross–Konno procedures were undertaken subsequently as repeat interventions—in fact, a total of 30. Overall outcome for these was 66% survival at 5 years. Now, of course there are reports of further improved survival with Ross–Konno procedures, and this may translate into a further bias towards management. However, at the same time as that survival will have improved with Ross–Konno procedures, survival also will have improved over the intervening decade with staged Norwood palliation, for example. So the only way of actually determining whether *index* Ross–Konno results in improved BVR survival is to undertake a contemporary investigation in which we enroll a higher proportion of Ross–Konno procedures and complex repairs. In fact, that is an investigation that the CHSS are looking at now with our latest LV outflow tract series.

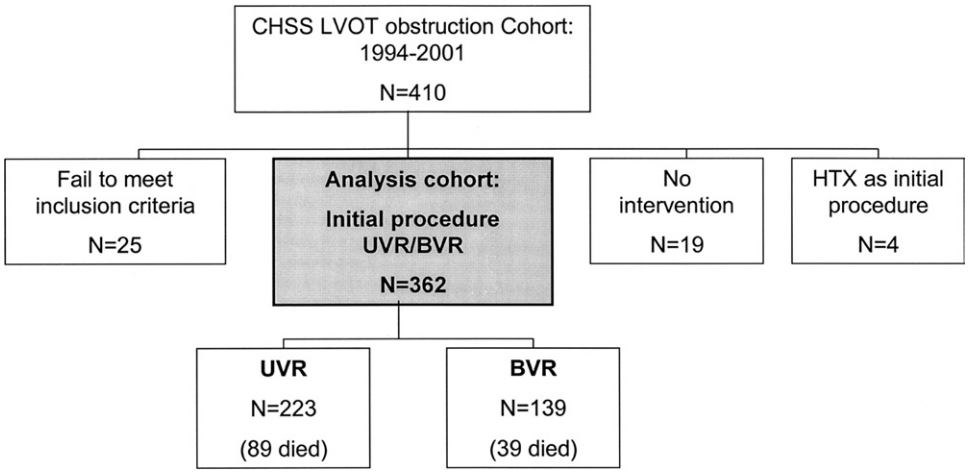

Figure E1. Algorithm indicating the profile of neonates with critical LVOT obstruction enrolled with the CHSS between 1994 and 2001. The present study analyzed the 362 neonates who underwent an index procedure (within age 30 days) indicating intended univentricular or biventricular repair. *HTX,* Heart transplantation; *UVR,* univentricular repair; *BVR,* biventricular repair; *LVOT,* left ventricular outflow tract; *CHSS,* Congenital Heart Surgeons' Society.

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

	Biventricular				Univentricular			
	n	Dead	m	Value	n	Dead	m	Value
Dead	139	39	0	39	223	84	0	84
General								
Male	139	31	0	118	223	53	0	156
BSA (m^2)	139	—	0	.225 (.12–.33)	223	—	0	.220 (.16–.30)
Weight (kg)	139	—	0	3.4 (1.3–6.1)	223	—	0	3.2 (1.9–5.4)
Age at intervention (d)	139	—	0	6.7 (0–30)	223	—	0	6.9 (0–29)
Procedural details								
Procedure type	139	—	0	—	223	—	0	—
Autograft AVR		3		5	—	—	—	—
Balloon aortic valvotomy		23		105	—	—	—	—
Surgical aortic valvotomy		12		27	—	—	—	—
Yasui procedure		1		2	—	—	—	—
Norwood palliation	—	—	—	—	223	84	0	223
Associated lesions								
Identifiable genetic syndrome	139	0	0	1	223	3	0	7
Noncardiovascular abnormality	139	3	0	6	223	7	0	14
Associated cardiovascular abnormality	139	2	0	6	223	6	0	14
Coarctation	129	7	10	17	191	31	32	72
Left SVC	139	1	0	1	223	11	0	27
Septum/endocardium								
ASD	108	10	31	24	171	24	52	69
VSD	117	4	22	8	183	20	40	45
VSD, large	116	2	23	4	172	8	51	13
EFE, grade	96		43		149		74	
0		7		48		23		63
1		11		39		21		59
2		3		6		7		24
3		3		3		1		3
LV function/size								
Grade of LV dysfunction	124		15		146		77	
Normal		6		53		10		32
Mild		4		11		14		36
Moderate		9		23		16		38
Severe		15		37		13		40
Ejection fraction (%)	50	—	89	47 (4–90)	11	—	212	40 (16–76)
Length of dominant ventricle (cm)	88	—	51	3.2 (2.4–4.4)	144	—	79	29 (18–41)
RV-forming apex	99		40	19	160		63	142
Rhodes score	86	—	53	−.4 (−4.2–1.9)	131	—	92	−2.8 (−5.5–.3)
Mitral valve								
MR, moderate or severe	122	9	17	20	216	57	49	7
MS, moderate or severe	115	18	24	35	200	55	23	147
Z-score MV annulus	108	—	31	−1.4 (−7.0–5.1)	187	—	36	−5.5 (−14.4–.47)
Tricuspid valve								
TR, moderate or severe	93	5	46	8	209	8	65	14
Z-score of TV annulus	77	—	62	−2.0 (−6.5–1.8)	137	—	86	−1.2 (−11.8–3.7)
Subaortic region/LVOT								
Sub-AoV stenosis	101	4	38	7	137	10	86	28
Sub-AoV diameter (cm)	91	—	48	.54 (.26–.87)	140	—	83	.38 (.18–.66)
AoV annulus (cm)	130	—	9	.59 (.37–.85)	202	—	21	.43 (.15–1.0)

TABLE E1. Continued

	Biventricular				Univentricular			
	n	Dead	m	Value	n	Dead	m	Value
Z-score of AoV annulus	130	—	9	−3.9 (−10.9–1.4)	202	—	21	−8.6 (−24.5–3.6)
AoV sinus diameter (cm)	91	—	48	.79 (.4–1.1)	146	—	77	.63 (.2–1.1)
Z-score at sinuses	91	—	48	−2.9 (−11.7–1.7)	146	—	77	−5.8 (−22.8–.22)
Sinotubular junction diameter (cm)	87	—	52	.72 (.4–1.2)	132	—	91	.52 (.2–1.0)
Z-score at sinotubular junction	87	—	52	−0.6 (−5.0–5.2)	132	—	91	−4.2 (−17.3–2.5)
Ascending aorta (cm)	108	—	31	.83 (.34–1.4)	208	—	15	.53 (.15–1.1)
Peak LVOT gradient	110	—	29	67 (4–174)	85	—	138	26 (0–87)
Mean LVOT gradient	72	—	67	41 (1–102)	51	—	172	14 (1–49)

*Institutional medical records were obtained that described patient demographics, pre-intervention echocardiography and angiography, procedural details, and autopsy reports where appropriate. Echocardiography recordings were requested and those obtained (n = 214) were examined independently by a blinded reviewer. Dimensional variables were standardized and expressed as z-scores on the basis of published normative data if available, or otherwise indexed to either body surface area or height. For risk-hazard analysis, missing values were imputed with the mean for that variable and a general missing value indicator created. This general missing value indicator was subsequently tested as a parameter in the regression analysis to refute the notion that patients with missing data may be different in terms of characteristics or risk from those in whom the data are not missing. Variables with excessive (>75%) missing values or associated with fewer than 5 deaths were suppressed during multivariate analysis to avoid the risk of over-determination. *AVR,* Aortic valve replacement; *BSA,* body surface area; *SVC,* superior vena cava; *ASD,* atrial septal defect; *VSD,* ventricular septal defect; *EFE,* endocardial fibroelastosis; *LV,* left ventricle; *RV,* right ventricle; *MV,* mitral valve; *MR,* mitral regurgitation; *MS,* mitral stenosis; *TR,* tricuspid regurgitation; *TV,* tricuspid valve; *AoV,* aortic valve; *LVOT,* left ventricular outflow tract; *n,* number of nonmissing values; *m,* number of missing values.

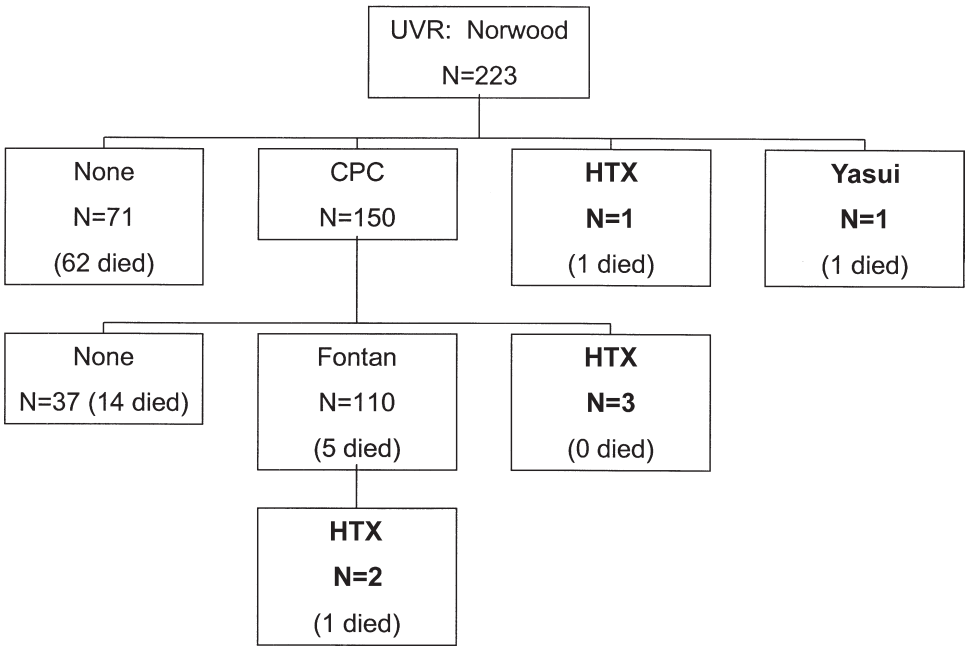

Figure E2. Subsequent procedures and mortality for patients who had an initial procedure indicating an intended univentricular management strategy. *Bold entries* represent "crossovers" (n = 7) to an alternative management strategy (BVR or transplantation) during the follow-up period. *UVR,* Univentricular repair; *CPC,* cavopulmonary connection; *HTX,* heart transplantation.

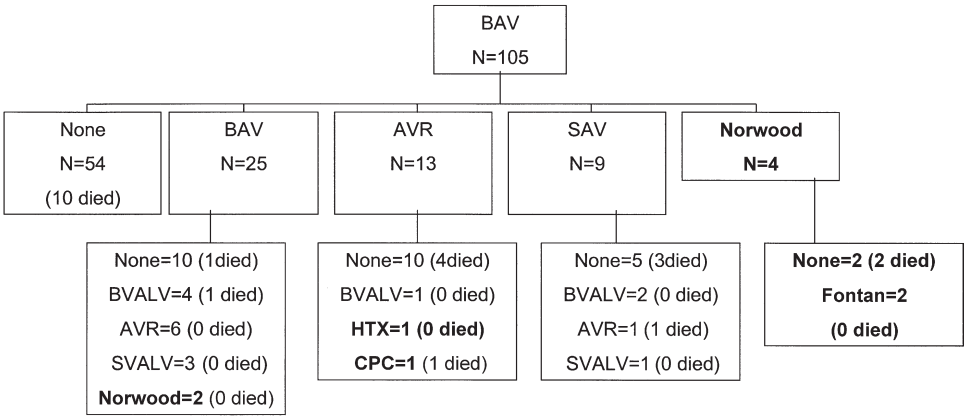

Figure E3. Subsequent procedures and mortality for neonates (n = 105) whose initial procedure was a balloon aortic valvotomy *(BAV). Italicized entries* represent "crossovers" (n = 7) to an alternative management strategy (UVR or transplantation) during the follow-up period. *AVR,* Aortic valve replacement; *SAV,* surgical aortic valvuloplasty; *HTX,* heart transplantation; *CPC,* cavopulmonary connection; *SVALV,* open surgical valvotomy; *BVALV,* balloon aortic valvotomy.

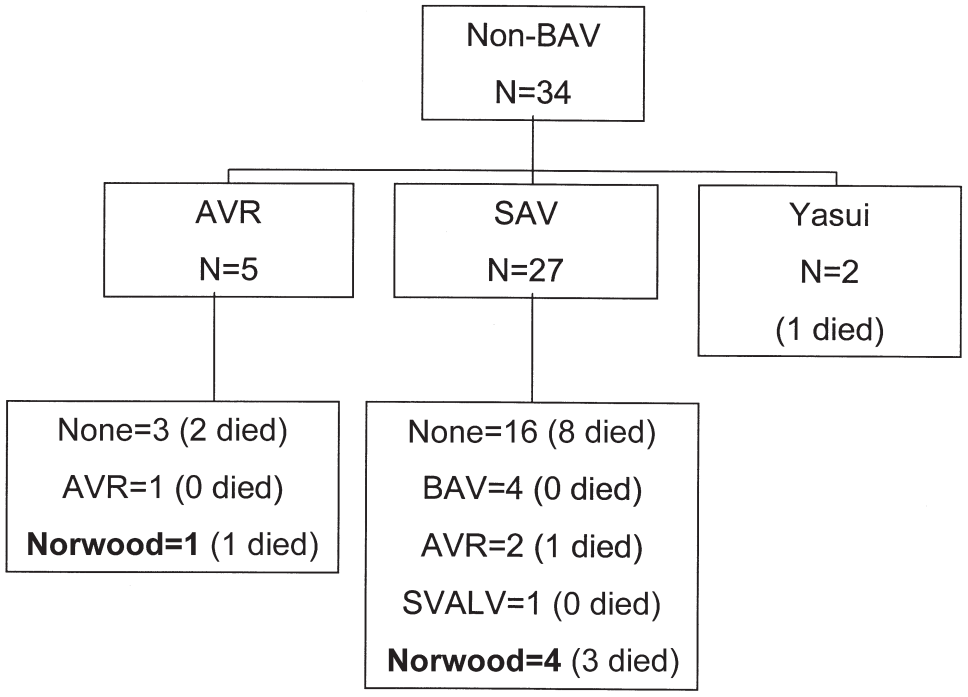

Figure E4. Subsequent procedures and mortality for patients who had an initial open surgical procedure indicating an intended BVR strategy. *Bold entries* represent "crossovers" (n = 5) to the opposite management strategy (BVR) during the follow-up period. *BAV,* Balloon aortic valvotomy; *AVR,* aortic valve replacement (Ross–Konno procedure); *SAV,* surgical aortic valvuloplasty; *SVALV,* open surgical valvotomy.

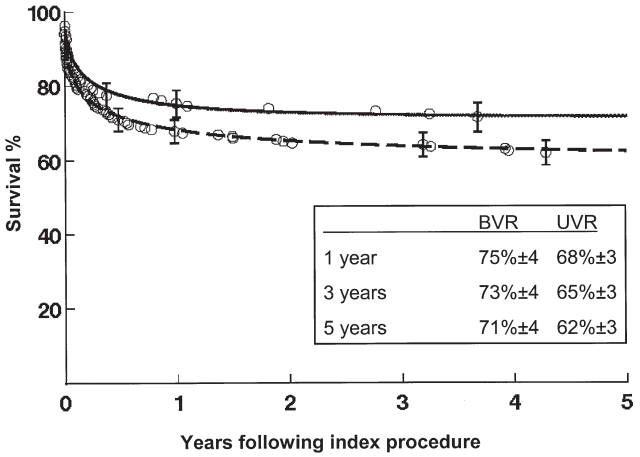

Figure E5. Unadjusted time-related survival plots for the study population stratified by intended management strategy. *Solid line* represents BVR (n = 139, 39 deaths). *Dashed line* represents UVR (n = 223, 84 deaths). *Circles* represent actuarial Kaplan–Meier estimates at events (deaths). *Lines* represent parametric continuous point estimates. The hazard domain for both BVR and UVR survival was only early, with no appreciable constant or late phases. Eighty-four percent of deaths had occurred within 1 year and 94% within 3 years. The difference in unadjusted survival between UVR and BVR did not reach statistical significance (*P* = .07). *Error bars* enclose 70% confidence intervals. *BVR*, Biventricular repair; *UVR*, univentricular repair.

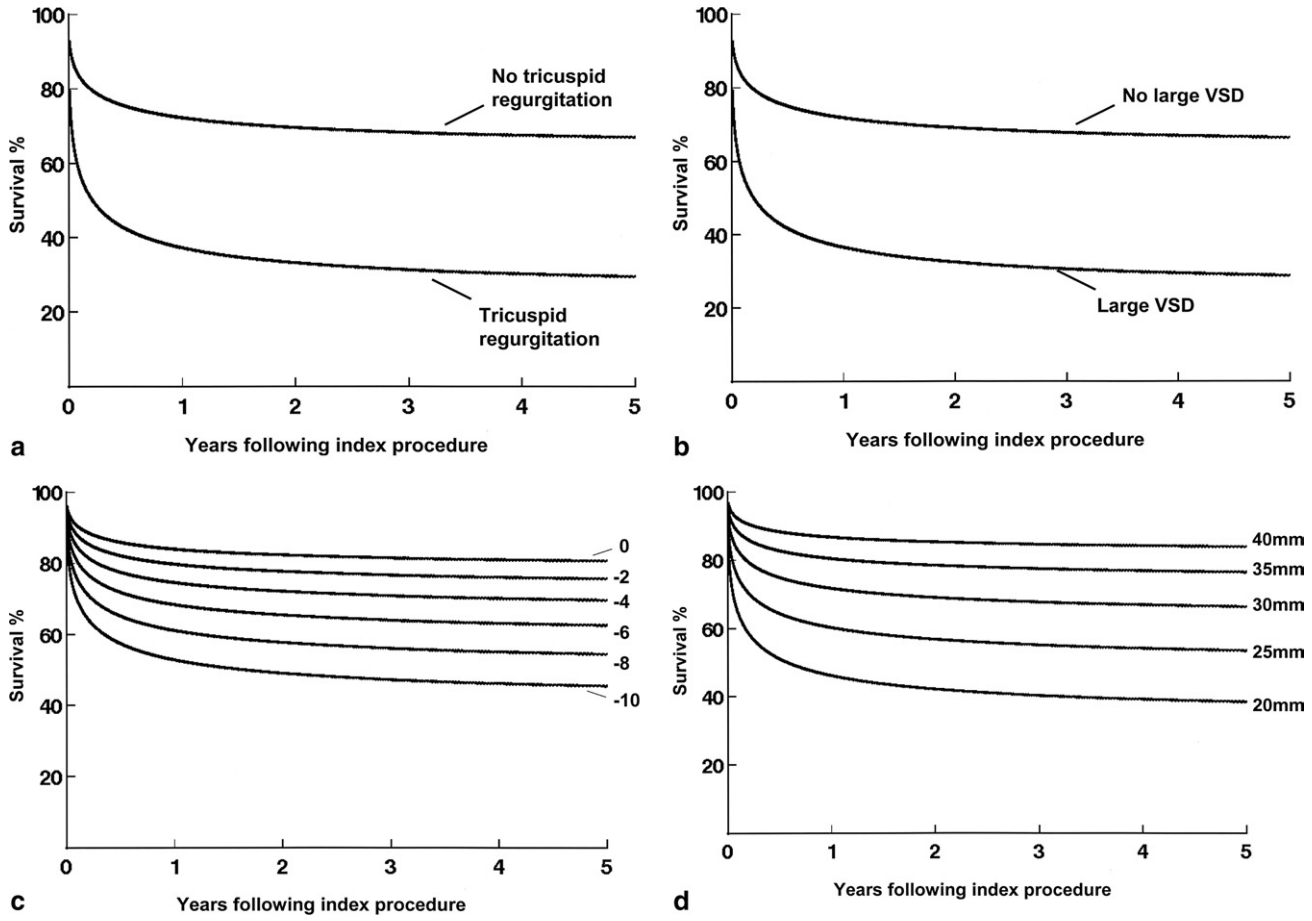

Figure E6. Risk-adjusted percentage survival after UVR (n = 223) stratified by (a) the presence of moderate or severe tricuspid regurgitation, (b) the presence of a large ventricular septal defect *(VSD),* (c) smaller mitral valve annular z-score, or (d) smaller indexed length of the dominant ventricle. For each stratified plot the remaining 3 variables are set at their mean value, and for the indexed length of the dominant ventricle stratifications are shown for values based on mean heights and weights. *Lines* represent the parametric determination of continuous point estimates of survival. *UVR*, Univentricular repair.

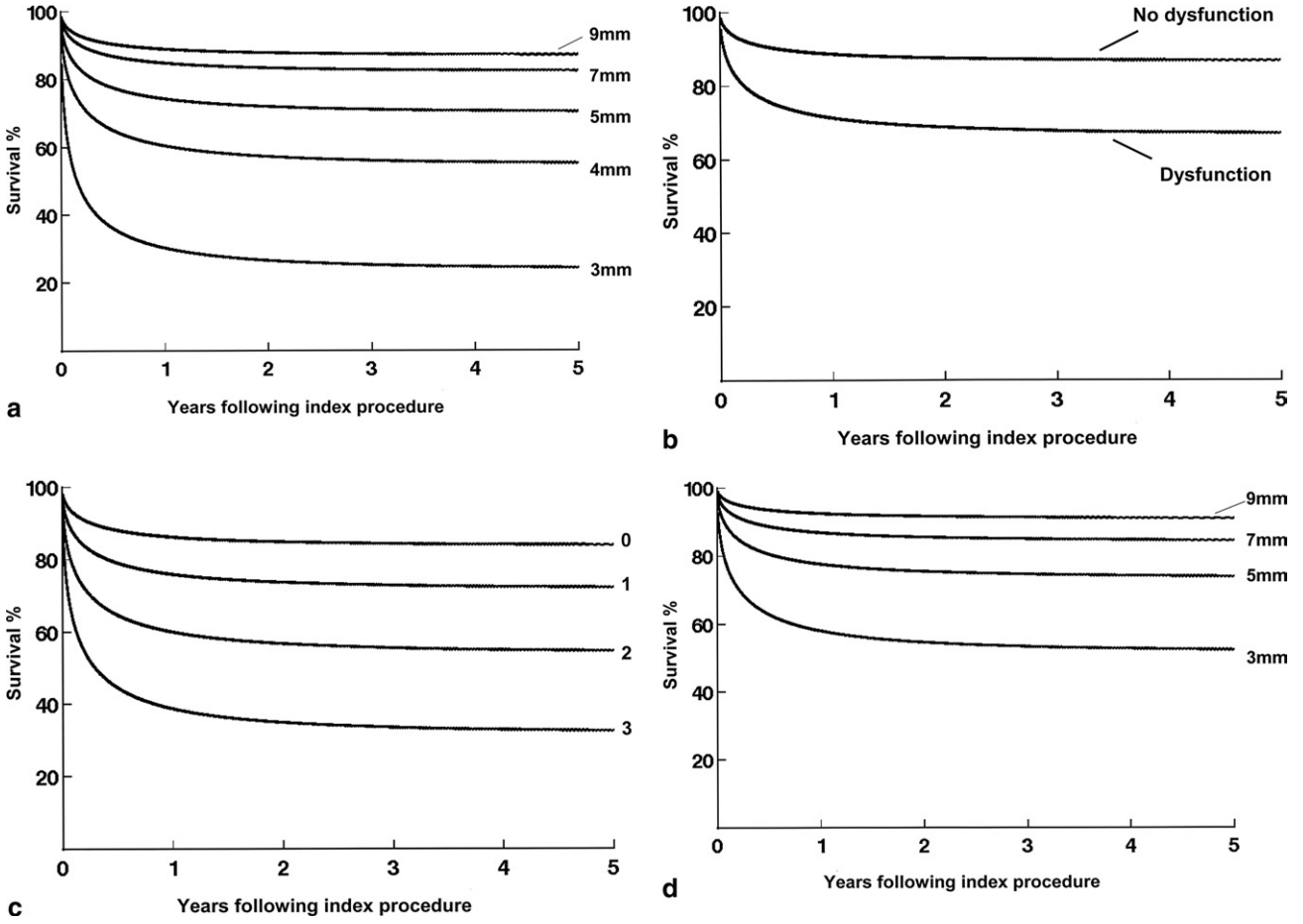

Figure E7. Risk-adjusted percentage survival after BVR (n = 139) stratified by (a) smallest indexed minimum diameter of the left ventricular outflow tract, (b) the presence of left ventricular dysfunction, (c) grade of endocardial fibroelastosis, or (d) indexed diameter of the transverse aortic arch immediately proximal to the left subclavian artery. For each stratified plot the remaining 3 variables are set at their mean value, and for indexed left ventricular outflow tract and arch diameters, stratifications are shown for values based on mean heights and weights. *Lines* represent the parametric determination of continuous point estimates of survival. *BVR*, Biventricular repair.