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

Edward J. Hickey, MD,[a] Christopher A. Caldarone, MD,[b] Eugene H. Blackstone, MD,[c] William G. Williams, MD,[b] Tom Yeh, Jr, MD,[d] Christian Pizarro, MD,[e] Gary Lofland, MD,[f] Christo I. Tchervenkov, MD,[g] Frank Pigula, MD,[h] Brian W. McCrindle, MD,[b] and the Congenital Heart Surgeons' Society

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)

CHD

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.

From the John Kirklin Fellow,[a] Congenital Heart Surgeons' Society Data Center, Toronto, Ontario, Canada; Hospital for Sick Children,[b] Toronto, Ontario, Canada; Cleveland Clinic Foundation,[c] Cleveland, Ohio; University of Texas Southwestern Medical Center,[d] Dallas, Tex; Alfred I Dupont Hospital for Children,[e] Wilmington, Del; Children's Mercy Hospital,[f] Kansas City, Mo; Montreal Children's Hospital,[g] Montreal, Quebec, Canada; and Boston Children's Hospital,[h] Boston, Mass.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 18, 2010; revisions received Aug 9, 2011; accepted for publication Sept 15, 2011; available ahead of print Feb 13, 2012.

Address for reprints: Brian W. McCrindle, MD, Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8 Canada (E-mail: brian.mccrindle@sickkids.ca).

0022-5223/$36.00

doi:10.1016/j.jtcvs.2011.09.076

Abbreviations and Acronyms

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

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