Predictors of Outcome of Biventricular Repair in Infants With Multiple Left Heart Obstructive Lesions

Marcy L. Schwartz, MD; Kimberlee Gauvreau, ScD; Tal Geva, MD

Background—Decisions regarding surgical strategy in patients with multiple left heart obstructive or hypoplastic lesions often must be made in the newborn period and are seldom reversible. Predictors of outcome of biventricular repair have not been well defined in this heterogeneous group of patients, and risk factors described for critical aortic valve stenosis have been shown to be inapplicable to patients with other left heart obstructive lesions. The goal of this study was to identify echocardiographic predictors of outcome of biventricular repair for infants with multiple left heart obstructive lesions.

Methods and Results—Patients with ≥2 areas of left heart obstruction or hypoplasia, diagnosed at ≤3 months of age, who had not previously undergone surgical or catheter intervention and maintained biventricular physiology were included (n=72). Failure of biventricular repair was defined as takedown to a univentricular repair, cardiac transplantation, and/or death (n=14; 19%). This group was compared with the patients who survived a biventricular approach (n=58). Multiple categorical, morphometric and calculated variables were examined on the basis of the initial echocardiograms. By multivariate analysis, predictors of failure included moderate/large ventricular septal defect (OR=22, P=0.001), unicommissural aortic valve (OR=16, P=0.006), and lower mitral valve dimension z-score (OR=2.2, P=0.02) or lower left ventricular end-diastolic volume z-score (OR=1.9, P=0.03).

Conclusions—Moderate/large ventricular septal defect, unicommissural aortic valve, and hypoplastic mitral valve or left ventricle are independent risk factors for failure of biventricular repair for infants with multiple left heart obstructive lesions. Combinations of these risk factors may be useful in selecting surgical strategy. (Circulation. 2001;104:682-687.)

Key Words: heart defects, congenital ■ echocardiography ■ risk factors

The management of patients born with multiple left heart obstructive or hypoplastic lesions is complex. A broad anatomic spectrum can be seen, ranging from mild lesions that may not require any intervention to severely obstructive or hypoplastic left heart anatomy that necessitates single-ventricle palliation. Decisions regarding surgical management often must be made in the newborn period. Because of the problems inherent with a single-ventricle (Fontan) palliation, including the usual need for multiple staged procedures and concerns regarding the long-term prognosis of a systemic right ventricle, a biventricular repair is thought to be preferable when possible.1 However, progressive, recurrent, or newly developed obstructive lesions, as well as persistent or progressive pulmonary hypertension, may complicate the clinical course after biventricular repair.2-4 Moreover, the early surgical strategy is seldom reversible. Some patients require takedown to a single-ventricle palliation or heart transplantation, but most patients who fail a biventricular approach ultimately die.5 This observation highlights the importance of selecting the appropriate management strategy in early infancy.

Predictors of outcome of biventricular repair have not been well defined in this heterogeneous group of patients, and risk factors described for critical aortic valve stenosis have been shown to be inapplicable to patients with other left heart obstructive lesions.6-11 The goal of this study, therefore, was to identify echocardiographic predictors of outcome of biventricular repair for infants with multiple left heart obstructive lesions.

Methods

Patients

The computer database of the Department of Cardiology at Children’s Hospital was searched for all patients born between January 1, 1988, and December 31, 1997, with multiple left heart obstructive lesions. Patients were considered for investigation if they presented to our institution at ≤3 months of age, had not undergone a surgical or catheter intervention before an initial echocardiogram, maintained biventricular physiology, and had 2 or more of the following areas of obstruction or hypoplasia: (1) mitral valve (MV): mitral stenosis (mean gradient >3 mm Hg), MV annulus hypoplasia, or parachute MV; (2) left ventricular outflow tract (LVOT): subaortic stenosis or LVOT diameter less than normal aortic annulus; (3) aortic valve:
aortic valve stenosis (maximum instantaneous Doppler gradient ≥20 mm Hg) or aortic valve annulus hypoplasia; (4) aortic arch: aortic arch hypoplasia, isthmic hypoplasia, coarctation, or interrupted aortic arch type A; or (5) left ventricle (LV): left ventricular–to–right ventricular (LV/RV) long-axis ratio <0.8 or small LV end-diastolic volume (LVEDV). Hypoplasia for each parameter was defined by a measurement with a z-score < −2.0, based on normative data from our institution. Patients who met only criteria 3 and 5 above (ie, only aortic valve stenosis or hypoplasia and LV hypoplasia) were not included, because this subset of patients was previously reported by Rhodes and colleagues. Patients were also excluded if they had mitral or aortic valve atresia, totally anomalous pulmonary venous connection, common atrioventricular canal defect, abnormal type of conal anatomy (transposition of the great arteries, truncus arteriosus, or double-outlet right ventricle), or interrupted aortic arch type B (because biventricular repair is seldom a clinical dilemma in these patients). The Committee on Clinical Investigations at Children’s Hospital approved the study protocol.

Outcomes

Patients were divided into 2 outcome groups. Failure of biventricular repair (failed 2V group) was defined as takedown to a univentricular repair (Norwood operation or bidirectional Glenn), cardiac transplantation, and/or death. This group was compared with the patients who did not fail a biventricular approach (successful 2V group).

A secondary outcome group was defined as a subset of patients from the successful 2V group. These patients had complicated clinical courses (complicated successful 2V group), defined as undergoing aortic or MV replacement or ≥5 interventional procedures. The complicated successful 2V group was compared with the failed 2V and uncomplicated successful 2V groups.

Echocardiography

Initial echocardiograms for all patients were reviewed. Categorical variables included presence of an atrial septal defect or patent foramen ovale, presence and type of ventricular septal defect (VSD), presence of a patent ductus arteriosus and direction of flow, presence of echogenic endocardium, left superior vena cava, parachute MV, mitral stenosis with a mean gradient of >3 mm Hg, aortic stenosis with a maximum instantaneous gradient ≥20 mm Hg, subaortic stenosis, and coarctation of the aorta.

Measurements of morphometric variables were made offline without knowledge of patient outcome. Lateral and anteroposterior mitral and tricuspid valve annulus dimensions were measured in diastole from apical 4-chamber and parasternal long-axis views. Mitral and tricuspid valve areas were calculated from lateral and anteroposterior dimensions by use of the formula for an ellipse (area = πD1D2/4). MV leaflet length was measured at end diastole from the apical 4-chamber view (Figure 1A). LV and right ventricular end-diastolic lengths and LV end-diastolic epicardial length were measured from the apical 4-chamber view (Figure 1A). LVEDV was calculated by the hemisphere cylinder (bullet) formula (V = 5/6 short-axis area × endocardial long axis). LV mass was calculated from the myocardial end-diastolic volume (epicardial volume−endocardial volume) × 1.05 g/mL. Diameters of the LV outflow tract, aortic annulus, root, and sinotubular junction were measured from the parasternal long-axis view in systole (Figure 1B).

Diameters of the ascending aorta (at the level of the right pulmonary outflow tract, aortic annulus, root, and sinotubular junction were measured from the apical 4-chamber view in systole (Figure 1B).

Results

Patients

Seventy-five patients met the above inclusion criteria. Three patients who died of noncardiac complications, including bowel malrotation, Allagille syndrome with biliary atresia, and a patient who died of sepsis after partial bowel resection, were not included in the analysis. Of the 72 patients analyzed, 14 (19%) required takedown to a univentricular repair or cardiac transplantation and/or died (failed 2V group) (Table 1). The successful 2V group was composed of the remaining 58 patients who survived with biventricular physiology. The
median age at time of first echocardiogram was 3 days (range 1 to 70 days) for the failed 2V group and 7.5 days (range 1 to 77 days) for the successful 2V group (P < NS). The mean weight was 3.2 ± 0.9 kg for the failed 2V group and 3.5 ± 0.8 kg for the successful 2V group (P = NS).

In the failed 2V group, 7 patients died after surgery. Five patients underwent takedown to a univentricular repair, resulting in 3 additional deaths, and 2 patients underwent cardiac transplantation with 1 subsequent death, for a total of 11 deaths (79% of failed 2V group) (Figure 2). The median time to first failure was 5 months (range 2 to 381 days) (Figure 3). For the 4 patients who required takedown to a univentricular repair or cardiac transplantation and then subsequently died, the median time between first failure and death was 1.5 days (range 0 to 19 days). The median follow-up time for the successful 2V group from the initial echocardiogram to December 31, 1999, was 5.9 years (range 2.0 to 12.1 years).

Predictors of Failure of Biventricular Repair

Variables associated with failure of biventricular repair for all study patients by univariate analysis included moderate/large VSD (P < 0.001), patent ductus arteriosus (P = 0.01), unicommissural aortic valve (P = 0.02), lower mean aortic root diameter z-score (P = 0.04), and lower mean distal transverse arch diameter z-score (P = 0.05). By multivariate analysis (Table 2), predictors of failure included moderate/large VSD (OR = 22, P < 0.001), unicommissural aortic valve (OR = 16, P = 0.006), and lower MV lateral dimension z-score (OR = 2.2, P = 0.02). The odds ratio for MV lateral dimension corresponded to a 1-Unit decrease in z-score. Alternatively, lower LVEDV z-score was also a significant risk factor for
failure in combination with moderate/large VSD and unicommissural aortic valve (OR = 1.9, P = 0.03). MV diameter and LVEDV were closely related, with a Spearman rank correlation coefficient of 0.47 (P < 0.001), and therefore both variables could not be included in the same multivariate model (Figure 4).

In addition to analysis of all patients, predictors of outcome were examined in the following subsets of patients.

Patients with MV involvement included those with mitral stenosis, hypoplasia, or parachute morphology (n = 33, 8 failed 2V group, 25 successful 2V group). For this subset of patients, by univariate analysis, the failed 2V group was associated with moderate/large VSD (P = 0.02), lower mean MV lateral dimension z-score (P = 0.02), unicommissural aortic valve (0.04), lower mean LV mass z-score (P = 0.02), and lower mean LV/RV long-axis ratio (P = 0.03). By multivariate analysis, predictors of failure of biventricular repair were the presence of a moderate/large VSD (OR = 40, P = 0.009) and lower MV lateral dimension z-score (OR = 15, P = 0.03).

Patients with LV hypoplasia, defined as LVEDV < −2.0 or LV/RV long-axis ratio of < 0.8, included 22 patients, 6 in the failed 2V group and 16 in the successful 2V group. By univariate analysis, failure of biventricular repair was associated with a moderate/large VSD (P = 0.009), higher mean aortic root and annulus z-scores (P = 0.03 and 0.04, respectively), and unicommissural aortic valve (P = 0.05). Increasing aortic annulus z-score was associated with increasing VSD size (P < 0.001, Figure 5).

Patients with aortic valve stenosis or hypoplasia included 47 patients, 11 in the failed 2V group and 36 in the successful 2V group. By univariate analysis, the failed 2V group was associated with moderate/large VSD (P = 0.006) and lower MV lateral dimension z-score (P = 0.02). By multivariate analysis, risk factors for failure of biventricular repair were moderate/large VSD (OR = 16, P = 0.01), unicommissural aortic valve (OR = 9.4, P = 0.04), and lower MV lateral dimension z-score (OR = 2.6, P = 0.03).

Because the presence of a moderate/large VSD was the strongest risk factor for the overall group of patients and for the subgroups, predictors of outcome were also examined separately in patients with moderate/large VSD and in patients with absent or small VSD. Patients with absent or small VSD (n = 53, 5 failed 2V) were more likely to fail biventricular repair if they had a unicommissural aortic valve (OR = 20, P = 0.02) or had lower MV lateral dimension (OR = 3.9, P = 0.04). For those patients with moderate/large VSD (n = 19, 9 failed 2V), 3 of 3 patients with a unicommissural aortic valve failed a biventricular approach, compared with 38% failure (6 of 16) without a unicommissural aortic valve (P = 0.09).

**Risk Factors in Combination**

Figure 6 shows the failure rates observed with combinations of the risk factors found to be significant by multivariate analysis. For example, patients with a moderate/large VSD in combination with a small LVEDV had an 80% failure rate, compared with 36% for patients with moderate/large VSD with a large LVEDV.

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**TABLE 2. Predictors of Failure of Biventricular Repair by Multivariate Analysis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/large VSD</td>
<td>0.001</td>
<td>22</td>
<td>(3.6, 136)</td>
</tr>
<tr>
<td>Unicommissural AoV</td>
<td>0.006</td>
<td>16</td>
<td>(2.2, 112)</td>
</tr>
<tr>
<td>Smaller MV annulus</td>
<td>0.02</td>
<td>2.2*</td>
<td>(1.1, 4.5)</td>
</tr>
<tr>
<td>Smaller LVEDV</td>
<td>0.03</td>
<td>1.9*</td>
<td>(1.1, 3.3)</td>
</tr>
<tr>
<td>Patients with MV involvement (n = 33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/large VSD</td>
<td>0.009</td>
<td>40</td>
<td>(2.5, 640)</td>
</tr>
<tr>
<td>Smaller MV annulus</td>
<td>0.03</td>
<td>15*</td>
<td>(1.4, 170)</td>
</tr>
<tr>
<td>Patients with AoV involvement (n = 47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/large VSD</td>
<td>0.01</td>
<td>16</td>
<td>(1.9, 139)</td>
</tr>
<tr>
<td>Unicommissural AoV</td>
<td>0.04</td>
<td>9.4</td>
<td>(1.2, 75)</td>
</tr>
<tr>
<td>Smaller MV annulus</td>
<td>0.03</td>
<td>2.6*</td>
<td>(1.1, 5.8)</td>
</tr>
<tr>
<td>Patients with small/absent VSD (n = 53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unicommissural AoV</td>
<td>0.02</td>
<td>20</td>
<td>(1.8, 232)</td>
</tr>
<tr>
<td>Smaller MV annulus</td>
<td>0.04</td>
<td>3.9*</td>
<td>(1.1, 14)</td>
</tr>
</tbody>
</table>

*Odds ratio corresponding to a 1-unit decrease in z-score.

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**Figure 2.** Outcome of 72 patients with multiple left heart obstructive lesions. Univent indicates takedown to univentricular repair.

**Figure 3.** Kaplan-Meier curve showing freedom from failure of biventricular repair over time. Number of patients at follow-up is noted in italics above years since repair.

**Figure 4.** Correlation of MV lateral dimension z-score with LVEDV z-score.

**Figure 5.** Risk Factors in Combining Multivariant Analysis

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Schwartz et al Outcome of Multiple Left Heart Obstructive Lesions 685

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and normal LVEDV. For patients with absent or small VSD, a 67% failure rate was seen for patients with both a small LVEDV and a unicommissural aortic valve. Within the group of patients with absent or small VSD, those with a hypoplastic MV and a unicommissural aortic valve had a 50% failure rate.

Interventions in the Successful 2V Group
For the 58 patients who survived a biventricular approach, 109 interventions were undertaken, averaging 1.9 interventions per patient (range 0 to 7 interventions). These included 25 interventional catheterizations, 33 open-heart operations, 47 coarctation repairs, 1 patent ductus arteriosus ligation, and 3 pacemaker implantations. The open-heart operations included 1 aortic valve replacement and 3 MV replacements (1 in the supra-annular position and 1 requiring subsequent transcatheter membrane oxygenation). In addition, 21 diagnostic catheterizations without intervention were performed.

Complicated Successful 2V Group
Five of 58 patients in the successful 2V group were identified as having a relatively more complicated clinical course, including aortic valve or MV replacement or ≥5 interventional procedures. There were no statistically significant differences between the complicated successful 2V group and either the failed 2V group or the uncomplicated successful 2V group. The complicated successful 2V group more closely resembled the uncomplicated successful 2V group. For example, 20% of the complicated successful 2V group had moderate/large VSD, compared with 17% of the uncomplicated successful 2V group and 64% of the failed 2V group.

Interobserver Variability
The interobserver variability of the echocardiographic measurements was examined in 55 patients by 2 independent observers. The mean (±SD) interobserver differences were 1.3±11.2% for lateral MV dimension, 8.8±28% for LVEDV, 3±10% for LV/RV length ratio, and 2.9±9.5% for the aortic valve diameter.

Discussion
This study identified the following echocardiographic parameters as independent risk factors for failure of biventricular repair in infants with multiple left heart obstructive lesions: moderate/large VSD, unicommissural aortic valve, and hypoplastic MV or left ventricle. The strongest risk factor was the presence of a moderate/large VSD. The reason for this observation is not clear. Although right-to-left systolic flow across a moderate/large VSD was more common in patients who failed a biventricular approach (5 of 9 patients compared with 3 of 10 patients), this observation does not fully explain why a moderate/large VSD is a risk factor for failure in these patients, nor does it explain the correlation between increasing VSD size and aortic valve size in the patients with LV hypoplasia (Figure 5).

Hypoplastic MV annulus was another independent risk factor for failure of the biventricular approach. Other morphological and hemodynamic abnormalities, however, such as parachute deformity, leaflet length, and Doppler gradient, were not predictive of outcome. The degree of mitral stenosis, as judged by the transmitral Doppler velocity, may be masked before surgery by several factors, such as a significant atrial septal defect with left-to-right flow or decreased cardiac output. Conversely, the size of the MV is less dependent on these factors and may represent the degree of MV stenosis or hypoplasia more accurately.

Although lower LVEDV was a risk factor for the overall group of patients, considerable overlap in LV size was seen between the 2 outcome groups. Like other investigators,5,9,10 we found several patients who survived a biventricular approach with LVEDV/BSA of 15 to 20 mL/m², well below the reported threshold value for patients with critical aortic valve stenosis.15

In addition to individual independent risk factors predictive of a failed biventricular approach, several combinations of lesions appeared to be predictive of poor outcome. For example, 80% of patients with a moderate/large VSD and LVEDV z-score <−2 were in the failed 2V group. Similarly, 57% of patients with a moderate/large VSD and a MV annulus z-score <−2 failed a biventricular approach. Moreover, the presence of a unicommissural aortic valve further increased the risk of failure in patients with any other independent risk factor.

Several authors have shown that the predictors of outcome for critical aortic stenosis cannot be reliably applied to patients with other left heart obstructions,6–11 but few have identified independent predictors for the more heterogeneous group with multiple left heart obstructive lesions.2,3,9 MV

Figure 5. Chart showing correlation between aortic valve annulus z-score and increasing VSD size. Horizontal bars denote mean aortic valve z-score for each VSD size category.
hypoplasia and stenosis have been associated with higher mortality after biventricular repair for patients with multiple left heart obstructions.\textsuperscript{2,3,9} Others have found preoperative pulmonary hypertension to be another important risk factor.\textsuperscript{2} Most of the patients in the present series underwent only noninvasive preoperative evaluation, and direct measurement of right ventricular pressure was frequently not available. As in previous studies,\textsuperscript{10,15} the 2 patients in this series who had only LV hypoplasia and aortic arch obstruction survived a biventricular approach. Similarly, no patient failed with only MV involvement and aortic arch obstruction (n = 10). Moreover, aortic arch hypoplasia and/or coarctation were universally present in this cohort and were not predictive of outcome. The presence of antegrade flow in the ascending aorta has been reported to be predictive of a successful biventricular approach.\textsuperscript{10,16} This observation, however, is not supported by this series. The majority of patients who failed a biventricular repair in this cohort (12 of 14 patients) had antegrade flow in the ascending aorta and transverse arch documented by Doppler echocardiography.

Limitations
The retrospective nature of this study imposed several inherent limitations. First, the technical quality of the echocardiograms varied. The good interobserver agreement in the key measurements, however, indicates that offline analysis of the echocardiograms was not a significant limitation. Second, the decision to pursue a single-ventricular or a biventricular strategy was made by individual cardiologists and surgeons. It is conceivable that some patients who underwent a single-ventricle palliation might have survived a biventricular approach. Conversely, it is not possible to know what the outcome of patients who failed a biventricular approach would have been if they had undergone a single-ventricle palliation. Third, use of survival as the only measure of outcome does not address morbidity. Some patients who survive a biventricular strategy may be left with a prosthetic MV, a pacemaker, and/or pulmonary hypertension. Finally, the long-term outcome of such patients remains to be determined.

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References
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