Predictors of Prosthesis Survival, Growth, and Functional Status Following Mechanical Mitral Valve Replacement in Children Aged <5 Years, a Multi-Institutional Study

Geetha Raghuveer, MD, MPH*; Christopher A. Caldarone, MD†; Christine B. Hills, BA‡; Dianne L. Atkins, MD§; John M. Belmont, PhD*; James H. Moller, MD‡

Background—Prosthesis survival, growth, and functional status after initial mechanical mitral valve replacement (MVR) in children <5 years of age are poorly defined.

Methods and Results—The experience of the Pediatric Cardiac Care Consortium (45 centers, 1982 to 1999), which included 102 survivors after initial MVR, was analyzed. Median follow-up: 6.0 years (interquartile range: 3.0 to 10.6 years; 96% complete). Twenty-nine survivors had undergone a second MVR at an interval of 4.8±3.8 years after initial MVR. Reasons for second MVR were prosthetic valve stenosis (83%), thrombosis (14%), and endocarditis (3%). For those who had second MVR, prosthesis sizes were: first MVR 19±2 mm and second MVR 22±3 mm, and their body weight increased from 7.4±2.8 kg to 16.8±10.5 kg. To identify risk factors for having a second MVR, the 29 second MVR survivors were compared with the 73 who did not have a second MVR on first-MVR demographic and perioperative variables. By univariate analysis, patients with shorter prosthesis survival were younger, weighed less, had smaller prostheses, greater ratio of prosthesis size:body weight, were less likely to have a St. Jude prosthesis and more likely to have Shone’s syndrome. By multivariate analysis prosthesis survival was predicted only by first MVR age: odds ratio (OR) 7.7 (95% confidence interval [CI] 2.6–22.7) and prosthesis size: OR 6.8 (95% CI 2.6–18.2). High risk patients (age <2 years and prosthesis size <20 mm at first MVR) had an OR = 46.3 compared with low-risk patients (age ≥2 years and prosthesis size ≥20 mm at first MVR) over similar follow-up intervals. Using first-MVR weight-matched controls, body weight increased similarly for patients <2 years old who had a second MVR versus those who did not. Prosthesis size, however, differed significantly, with second MVR patients having smaller prostheses at first MVR (18.7±0.8 mm versus 22.4±3.6 mm, P = 0.017). An estimate of current New York Heart Association (NYHA) functional status was class 1 in 76%, class 2 in 22%, and classes 3 or 4 in 2%.

Conclusion—Prosthesis survival can be predicted based on first MVR age and prosthesis size. Somatic growth is comparable regardless of the need for second MVR. There is an increment in prosthesis size at second MVR, suggesting continued annular growth. Significant limitation of function after MVR is uncommon. MVR may be an appropriate strategy for children <5 years old despite the risk of second MVR in the youngest patients in whom the smallest prostheses are used. (Circulation. 2003;108[suppl II]:II-174-II-179.)

Key Words: mitral valve replacement ■ outcome ■ growth ■ congenital heart disease ■ pediatrics

There is paucity of data addressing outcomes after mechanical MVR in children <5 years of age. In a young child with severe mitral valve disease after failure of mitral valve repair, alternatives to MVR and preservation of biventricular function would include single ventricle palliation with abandonment of the left ventricle, or cardiac transplantation. Choosing MVR over these alternatives is an attractive option if the probability of survival is high, the risk of second MVR is low, and functional outcome is satisfactory.

In a previous report from the Pediatric Cardiac Care Consortium,¹ we reported mortality and complications after initial MVR in this age group.² The predominant mortality after initial MVR occurred in the early postoperative period with little late attrition. Complications included permanent pacemaker implantation in 16%, bacterial endocarditis in 6%, and cerebrovascular accidents in 5%. An increased prosthetic valve size:body weight ratio, and the diagnoses of complete atrioventricular canal defect or Shone’s syndrome were predictors of perioperative death by multivariate analysis. Thus, by knowing diagnosis, mitral annulus size, and patient weight, the probability of survival after initial MVR could be estimated.

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If one were to choose MVR as a treatment strategy based on the probability of survival, the following questions for the potential survivors would need to be addressed: (1) what is the risk of needing a second MVR; (2) can this risk be predicted at the time of first MVR; (3) would a second MVR result in additional mortality and morbidity; (4) what is the effect of MVR on growth and functional status; and (5) does the rate of somatic growth influence the risk of second MVR? This paper addresses these questions and provides new information regarding the course of a large number of survivors of MVR performed under the age of 5 years.

Methods
The study population included all of the survivors of a first MVR performed before 5 years of age and reported to the Pediatric Cardiac Care Consortium by 45 participating institutions between January 1st 1982 and December 31st 1999. The patients demographic, perioperative (including second MVR if done), and other reports, which had been reported prospectively to the consortium, were reviewed. Patients were followed up, beginning January 1, 2000, by contacting the primary cardiologist to ascertain patient status and to obtain an estimate of the current functional status utilizing the NYHA functional classification.

Statistical Methods
Statistical analysis software was SPSS 9.0 (SPSS, Chicago, IL). Data are presented as frequencies, rates, and medians with interquartile ranges, mean ± SD, and survival curves. Tests of group differences included t-test, Mann-Whitney U, χ², and z-test, as appropriate. Estimates of median prosthesis survival times and 95% CIs were obtained by the Kaplan-Meier method. The Cox proportional hazards model was used to calculate prosthesis survival curves, and to test univariate and multivariate predictors of prosthesis survival.

Results
One hundred and eight children had survived >30 days after initial MVR at <5 years of age. Three survivors of first MVR proceeded to cardiac transplantation and were excluded from the analysis. Thirty-two patients underwent a second MVR, and 3 died after; these 3 were excluded from the analysis. Thus, there were a total of 102 first -MVR survivors (29 second-MVR survivors and 73 first-MVR survivors who have not had a second MVR at the time of follow-up) included in this analysis. Follow-up was 96% complete. Time from first MVR to follow-up: median=6.0 years (interquartile range, 3.0–10.6 years).

Mortality
Three patients died after a second MVR. One patient who had a second MVR performed for prosthetic mitral stenosis at age 16 (initial MVR was at age 4.6 years for severe mitral regurgitation) was placed on a left ventricular assist device after operation, and died 6 days later when the left ventricular assist device was removed. There were 2 late noncardiac deaths because of severe dehydration and stroke, respectively.

Cohort Having Second MVR
The 29 second MVR survivors had undergone a second MVR at an interval of 4.8±3.8 years after the initial MVR. The mean weight at first MVR was 7.4±2.8 kg, significantly below the 5th percentile for age.3 The mean weight at second MVR had increased to 16.8±10.5 kg (5th to 10th percentile for age). Prosthesis sizes were: first MVR 19±2 mm and second MVR 22±3 mm. Reasons for second MVR were: prosthetic valve stenosis 24 (83%), prosthetic valve thrombosis 4 (14%), and prosthetic valve endocarditis 1 (3%). Ten of the 24 who had second MVR for prosthetic valve stenosis were on inspection of the prosthesis noted to have fibrous tissue ingrowth and pannus formation. Four patients underwent resection of associated subaortic obstruction at the time of second MVR.

Predictors of Second MVR
The 29 second MVR patients are compared with the 73 nonreoperated survivors on first MVR demographic and perioperative variables (Table). Follow-up intervals from first MVR were 11.0±4.9 years for those patients who required a second MVR and 5.5±4.0 years for those who did not (P<0.001). Follow-up times were controlled for in subsequent analysis between the 2 groups.

The potential univariate predictors of second MVR (all from the time of first MVR) were younger age, lower weight, increased prosthetic valve size:body weight ratio, Shone’s syndrome, smaller prosthesis, and prosthesis other than St. Jude’s. The stepwise multivariate Cox regression yielded younger age at first MVR (OR 7.7, 95% CI 2.6–22.7), P=0.018, and smaller prosthesis at first MVR (OR 6.8, 95% CI 2.6–18.2), P=0.004, as significant predictors of second MVR.

Age at First MVR and Prosthesis Survival
The distributions of age at first MVR for patients who had a second MVR and for those who did not have a second MVR are shown in Figure 1. The distribution of age at first MVR of patients who required a second MVR was skewed (z=3.92, P<0.001), with 83% being <2 years of age at first MVR (only 5 of 29 being at least 2 years old). For patients who had not required a second MVR to date, age at first MVR was symmetrically distributed, with only 38% of patients being <2 years of age at first MVR. Based on these findings, age <2 years at first MVR was taken as the cut off for estimating the risk of second MVR.

Figure 2 shows the prosthesis survival curves for the entire cohort compared with that for patients ages <2 years old at first MVR and those ≥2 years old at first MVR. The 2 age-group curves differed significantly (P<0.001). Estimated median prosthesis survival for the younger age group was 7.8 years (95% CI: 5.4–10.2 years) compared with 12.7 years (95% CI: 7.2–18.3 years) for the entire group. Median prosthesis survival for the older age group could not be estimated as survival remained >50%.

Prosthesis Size at First MVR and Prosthesis Survival
The distribution of prosthesis sizes at first MVR for patients who had a second MVR and for those who did not have a second MVR are shown in Figure 3. The distribution of prosthesis sizes at first MVR for those who underwent a second MVR were skewed (z=2.26, P=0.012), with 76% having received a <20 mm prosthesis at first MVR (only 7 of
29 received prostheses ≥20 mm). For patients who had not required a second MVR to date, prosthesis sizes at first MVR was symmetrically distributed, with only 32% of the patients having received a <20 mm prosthesis at first MVR. On the basis of these findings, prosthesis size ≥20 mm was taken as the cut off for estimating the risk of second MVR.

Figure 4 shows the prosthesis survival curves for the entire cohort compared with that for patients with prosthesis size <20 mm at first MVR. The 2 prosthesis-size curves differed significantly (P<0.001). Estimated median prosthesis survival for the smaller prosthesis group was 6.3 years (95% CI: 4.1–8.6 years) compared with 12.7 years (95% CI: 7.2–18.3 years) for the entire group. The median prosthesis survival for the larger prosthesis group could not be estimated as survival remained >50%.

**Combined Risk of Age and Prosthesis Size at First MVR**

In order to reconcile the expected interaction between patient age and prosthesis size, we defined 3 risk groups. A high-risk patient was defined as first MVR age <2 years and first MVR prosthesis <20 mm (n=32). A medium-risk patient was defined as having 1 of these risk factors (n=33). A low-risk patient was defined as having neither risk factor (n=37). Follow-up times did not differ significantly among these three groups (high-risk group 8.0±5.1 years, medium-risk group 7.2±5.3 years, low-risk group 6.1±4.5 years; 0.001).

<table>
<thead>
<tr>
<th>Demographic and Perioperative Variables at the Time of 1st MVR for Those Who Had a 2nd MVR and Those Who Did Not</th>
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<tr>
<td><strong>Had 2nd MVR (n=29)</strong></td>
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<tr>
<td><strong>Demographic variables</strong></td>
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<td><strong>Pre-operative variables</strong></td>
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<td><strong>Pre-operative variables</strong></td>
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<td>Prosthesis other than St Jude (%)</td>
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<td>Leaflet sparing (%)</td>
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<td>Suprannular placement (%)</td>
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*By univariate Cox regression on prosthesis survival time. †AV means atrioventricular.

**Figure 1.** Age distributions at first MVR. A, patients who have undergone second MVR; B, those who have not.

**Figure 2.** Prosthesis survival for the total group compared with prosthesis survival in patients <2 yr old and ≥2 yr old at first MVR.
However, the risk of second MVR over these follow-up intervals differed significantly (high-risk 56.3%, medium-risk 30.3%, low-risk 2.7%, P<0.001). Relative to the low-risk group, ORs for the high- and medium-risk groups were 46.3 and 15.7, respectively. Figure 5 shows the prosthesis survival curves for these 3 risk groups. Median prosthesis survival time for high-risk patients was 6.3 years (95% CI: 1.0–11.6 years) and for medium-risk patients, 11.3 years (95% CI: 7.4–15.3 years). Median prosthesis survival for low-risk patients was indeterminate, as the failure rate was low. The overall risk effect was significant (P=0.001) and all 3 of the prosthesis survival curves differed significantly from one another (P<0.04).

MVR and Relations to Growth
Within the sample of patients who were <2 years old at first MVR and were followed for at least 5 years, 7 patients who had a second MVR (cases) could be matched within 300 g of first MVR body weight with 7 patients who did not receive a second MVR (controls). This was done to ascertain differences in weight gain if any, given an equal opportunity to grow. For each case-control pair individually, the case prosthesis survival time was taken as the target interval. For the corresponding control, the 2 weights recorded nearest to the post-first MVR target interval were used to interpolate the expected weight at target interval. Cases and controls had been followed for 9.2±4.2 years and 8.7±2.3 years, respectively (P=0.795). Figure 6 shows the case-control weight gains over their pair-matched target intervals. For cases and controls, respectively, weight at the beginning of the interval was 7.0±2.2 kg and 6.9±2.2 kg. Weight gains over the matched target intervals were 6.4±2.5 kg and 7.8±1.9 kg for cases and controls, respectively (P=0.282). Thus, no differences in rate of weight gain were observed among those requiring a second MVR. By contrast, first MVR prosthesis size was smaller for those requiring a second MVR (18.7±0.8 mm versus 22.4±3.6 mm; P=0.017).

Functional Status after MVR
An estimate of the current functional status as defined by the NYHA functional classification was provided by the primary cardiologist for 85% of the patients (Figure 7). Sixty-six (76%) of the sample were reported to be in NYHA class 1. Fewer second MVR patients were reported to be in NYHA class 1, and only 14% of patients who had not had second MVR patients were reported to be in NYHA class 1.

**Figure 3.** Distributions of prosthesis sizes at first MVR. A, patients who have undergone second MVR; B, those who have not.

**Figure 4.** Prosthesis survival for the total group compared with prosthesis survival in patients whose first-MVR prosthesis were <20 mm and ≥20 mm.

**Figure 5.** Prosthesis survival in the 3 risk groups (high-risk: age ≤2 yr and prosthesis size <20 mm at first MVR; medium-risk: age <2 yr and prosthesis size ≥20 mm at first MVR or age ≥2 yr and prosthesis size <20 mm at first MVR; low-risk: age ≥2 yr and prosthesis size ≥20 mm at first MVR).
MVR were classified as NYHA class 2. Overall, significant limitation of function (NYHA classes 3 or 4) was uncommon.

Discussion

The course of children undergoing MVR under the age of 5 years is largely unknown. In this article, we describe new and important information on a large number of survivors of this procedure using a multi-institutional database. Because MVR is performed infrequently, individual institutional experiences are often limited. Reports 4–9 are frequently from single institutions and are limited either by small sample size or short duration of follow-up. MVR in this age group is perceived to result in adverse outcomes, and management decisions are often based on these perceptions. In a growing child the durability of a fixed sized prosthesis is an added concern, as well as the potential for incremental mortality and morbidity at the inevitable second MVR. Whereas operative mortality after second MVR in our report was low (only 1 early cardiac related death), survival and other outcomes should be taken into account in order to optimize management strategies.

Risk of Second MVR

Young age and small prosthesis size at first MVR were significant predictors of prosthesis survival in our analysis, and this pattern was present even after controlling for differences in follow-up time. Whereas there is a constant risk of second MVR over time and with longer follow-up, eventually many more survivors can be expected to require replacement of their original valve prosthesis, the risk is highest in patients who are <2 yr and receiving prostheses <20 mm at initial MVR. Furthermore, body weight increase, per se, does not determine prosthesis survival in the high-risk cohort aged <2 years at first MVR, but the risk seems related to having received a smaller prosthesis at first MVR. We speculate that myocardial inflammatory or immunologic responses to prosthesis results in varying degrees of fibrosis, pannus formation, and narrowing of the effective orifice, maybe to a greater degree in patients with the smallest prosthesis. This effect may be akin to homograft survival variability that has been noted in different individuals and age-groups.10 Unfortunately, the clinician often has little ability to change the age or size of the patient requiring MVR, as these patients are often quite symptomatic. Thus, the variables identified as risk factors for second MVR are useful for prognosis, but not likely to be modifiable to a significant degree by the clinician.

We previously reported survival data after initial MVR in this cohort and showed that discrepancy between prosthesis size and body weight was a predictor of outcome, with larger discrepancies (greater prosthetic valve size:body weight ratio) being associated with higher early mortality.2 We proposed that patients could be chosen for or against the MVR strategy based on these projected mortality risks. A “larger prosthesis” than needed is often not chosen deliberately but rather because of lack of availability of “smaller prosthesis”. Whereas these “smallest available prostheses” may have been “large” at the time of initial MVR, resulting in the observed higher mortality, normalization of growth in these patients changes the prosthesis size:body weight ratio over time. Thus, recipients who are the youngest with the smallest prosthesis have more potential to “outgrow” the prosthesis because they are on the steeper slope of the growth curve.

MVR and Relations to Body Weight and Mitral Annulus

It has been reported previously that the need for second MVR is related to growth and increase in body weight.13 The relation between the rate of increase in body weight and the need for second MVR was additionally delineated in our study. No significant difference in rate of weight gain among the patients who had second MVR was observed (Figure 6); however, those who had a second MVR had received a smaller prostheses at first MVR.

FIGURE 6. Weight gain between first and second MVR (cases) or between first MVR and surrogate interval (controls) among 7 pairs matched for first MVR weight.

Figure 7. Estimate of current NYHA functional status among those who have undergone second MVR and those who have not.
an advantage in prosthesis survival, and we have noted previously no survival advantage either.\textsuperscript{2}

A larger prosthesis could be used at second MVR, suggesting that there is continued mitral annular growth despite being fixed to a prosthetic ring. This concurs with observations made in animal experiments\textsuperscript{12} and case reports.\textsuperscript{13}

Functional Outcome
Perceived functional outcome after MVR is good, and our results compare favorably with other reports.\textsuperscript{8,9,14} Despite the need for anticoagulation, patients appear to thrive after MVR with little significant functional limitation. The greater functional impairment in the second MVR group may be related in part to the need for repeat hospitalizations for cardiac catheterizations and surgery. Though longer follow-up is necessary to ascertain functional outcome as these children grow into adolescence and young adult years, preservation of biventricular function would appear to be an advantage.

In conclusion, our report describes 6-year outcome in a large cohort after initial MVR in patients <5 years of age. Prosthesis survival, like patient survival, can be predicted in these high-risk subsets, and included in counseling and estimating risk at the outset. Somatic growth is favorable after MVR and mitral annular growth appears preserved. Patients aged <2 years with a prosthesis size <20 mm at initial MVR have a shorter interval to second MVR. In this high-risk subset, the need for second MVR is determined by small initial prosthesis rather than “outgrowing” of the prosthesis because of increase in body weight per se. Significant functional limitation is uncommon despite second MVR. This risk of second MVR and functional outcome along with previously published mortality risk may help providers in developing an appropriate management strategy for patients <5 years of age with nonrepairable mitral valves. It is prudent to compare these outcomes and benefits of a preserved biventricular function to outcomes following other palliative strategies that are often offered to these high-risk subsets, namely single ventricle palliation and/or cardiac transplantation.

Limitations
Though the pertinent data had been reported by individual institutions to the Pediatric Cardiac Care Consortium prospectively, this is a retrospective analysis and, hence, subject to inherent deficiencies, including reporting bias, and limitations and errors in data collection. Of particular importance was the unavailability of data like severity of symptoms, transmirtal gradients, and pulmonary artery pressures on which the decisions to proceed with second MVR were made. However, it can be inferred that the majority of patients had a second MVR because of significant, symptomatic, prosthesis:body size mismatch. A prospective study examining prosthesis survival and growth in those <2 yr of age at initial MVR will provide more meaningful information about the association among age, prosthesis size, growth, and prosthesis survival. Functional status, as perceived by the provider, is at best an estimate, and detailed standard scales are likely to be more accurate in assessing subjective well-being, functional status, and quality of life in older children.

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References
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