Long-term follow-up after mitral valve replacement in childhood:
poor event-free survival in the young child§

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Abstract

Objective: In children, mechanical mitral valve replacement may be the only option if the failing mitral valve cannot be repaired. Mandatory anticoagulation and the fixed size prosthesis are of concern in the growing child, but long-term follow-up results are lacking. Methods: Single centre, extended retrospective study of 54 patients who underwent first mitral valve replacement between June 1982 and December 1997. Median age at operation was 3.0 years (range 2 days—18.1 years), 21 patients were ≤ 2.0-year-old. Mitral valve replacement was performed for congenital (43 patients) or acquired (11 patients) heart disease. Median follow-up for operative survivors was 9.2 years, with follow-up > 15 years (maximum 22 years) in nine patients. Results: Thirty-day mortality was 42% in patients ≤ 2-year-old, and 6% in older patients. There were 10 late deaths. Estimated survival at 10 and 15 years follow-up was 33% ± 19% and 33 ± 27% in patients ≤ 2-year-old, and 81% ± 8% and 75% ± 16% in older patients, respectively. High operative mortality in the younger age group was the most important contributor to poor long-term survival. Fifteen patients underwent redo-mitral valve replacement with one operative death. A larger valve was always implanted. Freedom from redo-mitral valve replacement at 10 and 15 years was 25% ± 22% and 0% in patients with prostheses < 23 mm, and 83% ± 13% and 83% ± 27% in patients with larger prostheses. Significant bleeding events occurred in eight patients and were often associated with operative interventions. Estimated freedom from bleeding was 75.7% ± 9% and 70.6% ± 16% at 10 and 15 years, respectively. Thromboembolism and endocarditis were rare. There was no structural valve failure. Estimated freedom from all adverse events at 10 years follow-up was 17% ± 13%. Conclusions: At 10 years follow-up after mechanical mitral valve replacement, most children had suffered an adverse event. At 15 years, all children with a prosthesis < 23 mm had outgrown their valve, but redo-mitral valve replacement with a larger size prosthesis was always possible, and carried low operative risk. Long-term anticoagulation was well tolerated. In children every effort should be made to preserve the native valve.

Keywords: Mitral valve replacement; Child; Long-term follow-up

1. Introduction

Mitral valve failure in children is rare and most commonly related to a congenitally abnormal mitral valve. Mitral valve repair is the preferred treatment, but this is not always possible, and mitral valve replacement (MVR) may be the only option. Because bioprosthetic mitral valves in children are subject to early calcification, mechanical prostheses are favoured [1] even though they require life long anticoagulation.

We previously reported short and medium-term outcome for 54 consecutive patients that underwent mechanical MVR at our Institution up to a medium follow-up time of 4.1 (maximum 11.3) years [2,3]. This study showed that MVR in children is associated with a high complication rate, in particular related to high peri-operative mortality in the very young child, the mandatory anticoagulation and the need for repeat MVR for patient/prosthetic size mismatch as the child grows. Other publications have shown similar findings [4,5]. Little is known, however, on the long-term outcome. We therefore performed an extended follow up study in this group of patients.

2. Patients and methods

For the initial study, follow-up data were collected on 54 consecutive patients who underwent MVR between January 1987 and December 1997. End date for data collection was 31 October 1998. For the current study, data collection was extended to 31 October 2005.
There were 29 girls and 25 boys with a median age of 3.0 years (range 2 days–18.1 years) at the time of first MVR. Twenty-one patients were <2-year-old. Median body weight was 12.1 (3.2–44.7) kg. Indication for MVR was mitral valve (left atrioventricular valve) regurgitation in 32 patients, mitral stenosis [10], mixed mitral valve disease [4], vegetations [3], and redo-MVR for prosthetic mitral stenosis [5]. The latter five patients received their first MVR prior to 1987 (earliest in 1982). Because this study is patient based, details on these five patients were entered from their first MVR, rather then taken from the time of redo-MVR as was done in our previous report that reported on outcome after MVR performed in a particular time-period [2].

The cardiac diagnoses are summarised in Table 1. Associated cardiac defects were present in 37% of patients [2]. All patients received a mechanical valve. The surgical technique has been described previously [2], and in short involved operation on cardiopulmonary bypass with use of cardiopulmonary arrest. The aim was to preserve the posterior mitral leaflet with supporting chordal apparatus, but this was only possible in a few cases. In many patients with congenital mitral valve disease, the structure of the subvalvar apparatus was abnormal and required excision to achieve unobstructed left ventricular inflow, or to create space for insertion of an adequate size prosthesis. In eight patients the valve was sutured in the supraannular position because the native valve ring did not admit the smallest available prosthesis. Anticoagulation was with sodium warfarin, aiming at an international normalised ratio of 2.5–3.5, and more recently between 2.0 and 3.0. Temporary anticoagulation with intravenous heparin was used during invasive or dental procedures, aiming at a partial thromboplastin time ratio between 1.5–2.0 times above baseline. Lately low molecular weight heparin has also been used in situations where warfarin was contra-indicated. Antiplatelet drugs were not routinely prescribed. The study was approved by the local research and ethics committee.

Patients were followed up by the paediatric, adult, or adult congenital cardiology services. Details were obtained from review of the case notes and from contacting the patient’s cardiologists and general practitioners. The end date for data collection was 31 October 2005. Patients who had not been seen in the 2 years prior to closing date were declared lost to follow-up. Follow-up was complete for the immediate post-operative period. Seven patients (four from Europe and three from outside Europe) had been reported as lost to follow-up during the initial study, and a further two (both from the United Kingdom) were lost during the extended study period. For these nine patients data were included in the analysis until their last documented follow-up. The cumulative follow-up was 401.1 patient years with a median follow-up of all operative (≥30 days) survivors of 9.2 years. Nineteen patients were followed up for more than 10 years, and 9 for more than 15 years, with maximum follow-up of 22 years.

### 2.1. Data handling

Results are presented as absolute numbers (with percentage where appropriate) or as median with outer ranges. The Kaplan–Meier method was used to estimate long-term survival and freedom from adverse events. Subgroups were tested with a two-tailed χ²-test with Yates’ correction for significant differences, and the U-test according to Wilcoxon, Man and Whithney was applied to test continuous parameters for significance. Statistical significance was set at p < 0.05.

### 3. Results

#### 3.1. 30-Day mortality and late deaths

Eleven patients (20%) died within 30-days of operation, nine patients were ≤2-year-old (mortality 42%) and two patients (mortality 3%) >2-year-old (p < 0.001). In eight patients the case of death was cardiac related [2]. There were 10 late deaths (Table 2). Estimated survival at 10 and 15 years follow-up was 33% ± 19% and 33% ± 27% in patients ≤2-year-old, and 81% ± 8% and 75% ± 16% in older patients, respectively. Survival is depicted in Fig. 1. The high 30-day mortality was the most important contributor to the poor long-term survival in the youngest age group.

#### 3.2. Cardiac transplantation

Three patients underwent cardiac transplantation and all are currently alive. One patient had congenital mitral regurgitation and suffered severe cardiac failure immediately after MVR necessitating ECMO support. Mechanical support was weaned but she required transplantation for severe cardiac failure four months later. A further patient with dilated cardiomyopathy and mitral regurgitation secondary to viral myocarditis was transplanted 8.5 years following MVR. He developed graft failure and underwent successful redo-transplantation. A third patient with a Shone’s type syndrome (congenital mitral stenosis, subaortic

### Table 1

Table 1. Causes of late death (>30 days) after mitral valve replacement

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Time since 1st MVR (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post redo MVR 1</td>
<td>6.9*</td>
</tr>
<tr>
<td>Valve thrombosis + pregnancy</td>
<td>8.3*</td>
</tr>
<tr>
<td>(non-compliant with medication)</td>
<td></td>
</tr>
<tr>
<td>Multi-organ failure post MVR 2</td>
<td>0.2 and 0.3</td>
</tr>
<tr>
<td>Chronic heart failure 2</td>
<td>0.7 and 5.9*</td>
</tr>
<tr>
<td>Sudden 2</td>
<td>1.1 and 16.7*</td>
</tr>
<tr>
<td>Unknown 2</td>
<td>3.0* and 13.0*</td>
</tr>
</tbody>
</table>

* Died in the last 7 years.
stenosis and a borderline size left ventricle) was transplanted 19.3 years after MVR. The patient developed B-cell lymphoma, received chemotherapy and is currently in remission.

3.3. Redo-MVR

Fifteen patients required redo-MVR. There was one operative death. Three patients subsequently underwent second redo-MVR. In all patients, the indication for redo-MVR was patient/prosthetic size mismatch. First redo-MVR was performed at a median of 7.5 (2.2—13.0) years following the initial MVR. Fig. 2 depicts valve size and make in patients that underwent MVR and repeat MVR. At first redo-MVR, eight tilting disc and seven bileaflet prostheses were replaced, all with bileaflet prostheses, and an increase in at least one valve size was always possible. Three of these patients (valve size 19, 19 and 23 mm) subsequently required further replacement with a larger bileaflet prosthesis (23, 21, 25 mm) after 7, 9 and 12 years, respectively. No patient required redo-MVR for paravalvular leak, inappropriate positioning or haemolytic anaemia.

Timing of redo-MVR was guided by clinical symptoms and echocardiographic findings of prosthetic mitral stenosis. However, there was poor correlation between symptoms (in decreasing frequency: diminishing exercise tolerance, shortness of breath, chest infection, and syncope) and the severity of prosthetic mitral stenosis on echocardiography (in decreasing frequency: elevated transprosthetic mean gradient [up to 20 mmHg in most cases], pulmonary hypertension, enlarged left atrium and prolonged mitral inflow). At the time of redo-MVR surgery, a variable amount of pannus was seen on both the arterial and ventricular side of the prosthesis in all patients. This was interfering with the leaflet movement in two cases (one tilting disc and one bileaflet valve). At 13 years follow-up, all surviving patients who initially received a prosthesis <23 mm had undergone redo-MVR, however, for those with prostheses ≥23 mm, estimated freedom from redo-MVR was 82% ± 16% (Fig. 3).

3.4. Bleeding

Significant bleeding events were defined as those requiring intervention, hospital admission, or blood transfusion, and were reported on nine occasions in eight patients. Bleeding episodes were related to surgical interventions (particularly dental extractions) in four patients. Other cases were: spontaneous intraabdominal [1], intra-articular after trauma [1], gastrointestinal [1], cerebral [1] and severe nasal bleeding [1]. Many patients reported minor bleeding events like nose bleeds or bruising after trivial injuries, but these
events were not included in the statistical analysis. Estimated freedom from important bleeding events was 75.7% ± 9% and 70.6% ± 16% at 10 and 15 years, respectively.

3.5. Other valve-related complications

The incidence of other valve-related complications was low. One patient who died suddenly was found to have prosthetic valve thrombosis and unexpectedly also found to be pregnant. She was known to be non-compliant with her medication. Another patient suffered two episodes of amaurosis fugax.

There were three episodes of prosthetic mitral valve endocarditis in two patients. All episodes were successfully treated with antibiotics. A third patient, who required a permanent transvenous pacing system for complete heart block following MVR, developed lead endocarditis with vegetations on the tricuspid valve. The system was changed, but 2.5 years later, there was a further infection on the new system, which was successfully managed with antibiotics.

3.6. Freedom from all adverse events

Taking into account death, cardiac transplantation, redo-MVR, bleeding, thrombo-embolism, and endocarditis, the longest event-free survival in a patient was 13.8 years. Estimated freedom from adverse events at 5 and 10 years was 45.3% ± 11% and 17.3% ± 14%, respectively (Fig. 4).

3.7. Other significant events

3.7.1. Pregnancy

One patient was found to be pregnant at autopsy (already discussed). A further patient delivered a healthy baby without complications 9.3 years after MVR.

3.7.2. Cardiac arrhythmia and need for permanent pacemaker

Seven patients had complete heart block after their first MVR requiring a permanent pacemaker system. Six of these had congenital heart disease (atrioventricular septal defect [5] and subaortic stenosis [1]). Late implantation of a permanent pacemaker was required following surgery for redo-MVR at 5.8 years follow-up (one patient), and after resection of subaortic stenosis at 8.8 years follow-up (one patient). A further patient with restrictive cardiomyopathy had a pacemaker implanted at 10 years follow-up. Five patients suffered dysrhythmia without the need for a permanent pacemaker. These included first grade AV-block [1], permanent junctional rhythm [1], intermittent junctional rhythm [1], and atrial flutter [2]. One of the latter episodes was in the context of endocarditis and converted to sinus rhythm by cardioversion. No patient is currently in chronic atrial fibrillation.

4. Discussion

We previously reported one of the largest single centre studies of mechanical valve replacement in children with up to medium-term follow-up. In the current study, we report on a further seven years follow-up for this cohort. What can be learned from this new information?

With longer follow-up, it is becoming increasingly clear that there is an ongoing attrition of the population that underwent mechanical MVR in childhood. Whereas very few healthy children are expected to die in childhood, our initial study reported four late deaths and one cardiac transplant after a medium follow-up of 4.1 years. Seven years later, a further six patients have died and another two underwent cardiac transplantation. Although two of the new cases were expected — at the end of the initial study one patient with end-stage cardiac failure was receiving palliative care and another was awaiting cardiac transplantation — this was not the case for the remainder of the cases. Two of the deaths were prosthetic valve related (one thrombosed valve and one following redo-MVR), and further patient with a Shone’s type syndrome, required transplantation because of the underlying cardiac abnormality. In the other three cases, including one sudden death, the cause of death was unknown. However, it is likely that either a prosthetic valve related problem or cardiac failure contributed to at least some of these deaths. Although various studies up to medium-term follow-up suggest that the long-term survival for children after MVR is encouraging [4,5], a long-term follow-up study Erez et al. [6] supports our findings. At mean follow-up of 9.3 years, the author reported four late deaths and seven orthotopic cardiac transplants for cardiomyopathy. Given the heterogeneous study populations, small patient numbers and the retrospective nature of the studies, it is difficult to identify specific risk factors for the high incidence of cardiac failure following MVR. However, the following factors, alone or in combination, may play a role: congenital heart disease, multiple cardiac operations, failure to preserve the subvalvar mitral apparatus at the time of MVR, primary cardiomyopathy, or cardiomyopathy secondary to long-standing mitral valve disease.

As anticipated, the incidence of redo-MVR increased with longer follow-up. In our initial study five patients underwent redo-MVR and a further five had entered the study at the time of their second MVR. Over the next 7 years, redo-MVR was required in another five patients and three underwent repeat redo-MVR. The indication for redo-MVR was patient/prosthetic mismatch, and it was always possible to place a larger valve with low operative mortality. Similar findings were reported by others [5,7], and young age at initial MVR, and small prosthetic valve size have been identified as risk factors for redo-MVR [7]. In spite of increasing experience the
indication and optimal timing for redo-MVR for patient/prosthesis mismatch remains to be defined, and we continue to use a combination of clinical symptoms and echocardiographic findings of an increasing gradient over the prosthesis. As a measure of prosthetic mitral stenosis, a maximum transvalvar Doppler velocity of $>2.2 \text{ m/s}$ has been suggested [5]. Our observation that all prosthesis $<23 \text{ mm}$ eventually have to be replaced, may further add to the decision making.

Permanent anticoagulation appears to be well tolerated in that the incidence of significant bleeding and thromboembolic events was low, both in our study and in reports from many others. Interestingly, a teenager known to be non-compliant with her medication died suddenly and was found to have a thrombosed valve. With more patients growing up into adolescence, compliance with medication is likely to feature more prominently. This is well known for other adolescent patients that require mandatory maintenance medication, such as transplant recipients [8]. The problem may be further complicated by patients moving away from the parental home, and the interaction of warfarin with new food stuffs (such as alcohol) or other medication (such as the contraceptive pill). The use of anti-platelet agents rather then warfarin has been proposed as a simpler way to prevent thromboembolism. A recent prospective study by Khitin et al. [9] in 72 patients $<20\text{-year-old}$ that had mechanical valves implanted in the left side of the heart, did not detect a difference in the incidence of thromboembolic and bleeding events up to five years follow-up between patients that received antiplatelets drugs and those that received warfarin. However, bleeding events in those that used warfarin were more severe. Unfortunately, due to small patient numbers and short follow-up no firm conclusions can be drawn from this study.

This is a recurrent problem and to our knowledge there are currently no published studies that are powerful enough to give a definitive answer about the optimal anticoagulation regime for children with prosthetic valves.

The risk of thromboembolism is not only determined by the choice of valve prosthesis, but also influenced by patient characteristics. These characteristics change when the patient grows older. The reduction of baseline heart rate also slows prosthetic valve movement which may affect the ‘washing’ of the valve. Enlargement of the left atrium and onset of atrial fibrillation are known risk factors for thromboembolism, even in the absence of a prosthetic valve. The above would suggest that the optimal levels of anticoagulation for children and adults with prosthetic valves are likely to be different. However, this has not been formally investigated. The ability to maintain the desired level of anticoagulation within narrow limits is another important factor in the prevention of thromboembolic and bleeding events. Self prescription of warfarin with home monitoring of anticoagulation has been shown to be superior to general practitioner prescription [10], at least in the adult population. The presence of a prosthetic valve has many disadvantages in woman of childbearing age [11]. Pregnancy causes an important haemodynamic burden on the circulation, and ideally the circulation should be optimised as much as possible prior to planning conception. The use of warfarin during pregnancy is associated an increased incidence of spontaneous abortion and foetal embryopathy. The mother is exposed to an increased risk of bleeding, prosthetic valve thrombosis, thrombo-embolism and death. However, with careful anticoagulation management and intensive monitoring successful pregnancy and delivery of a healthy baby is possible, as was also shown in our series.

4.1. Limitations of the study

Retrospective studies are likely to under report events and thus the actual incidence of complications may be higher than reported in the study. Unfortunately, in our study nine patients were lost to follow-up, seven of these were from abroad. This is characteristic for our Institution where many overseas patients are treated. In addition, two patients from the UK were lost to follow-up since they reached adulthood and moved away, and could not be traced via their former general practitioners or cardiologists. The aim of the study was to investigate mortality and morbidity in patients after mechanical MVR, and therefore data on the five patients that entered the original study at the time of redo-MVR were entered from the time of their first MVR. This could potentially introduce some bias in the results of the study, since these five patients were operative survivors after their first MVR and thus the operative mortality and survival in the early years could have been underestimated in this report.

5. Conclusions

This long-term follow-up study showed that mechanical mitral valve replacement has many implications for the growing child. At 10 years follow-up most children had suffered an adverse event. At 15 years, all children with a prosthesis $<23 \text{ mm}$ had outgrown their valve, but redo-MVR with a larger size prosthesis was always possible, and carried low operative risk. Long-term anticoagulation was well tolerated in children, but is likely to be more problematic in the young adult. In children every effort should be made to preserve the native valve.

Acknowledgements

The authors are very sorry to report that Dr Wolfram Beierlein died in a car accident in May 2006. He greatly contributed to the collection of the extended follow-up data, data analysis and wrote the first drafts of this paper.

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Appendix A. Conference discussion

Dr M. Wojtalik (Poznan, Poland): This is a historical series of patients. Do you think that the current CardioChek system might improve the results or it depends on the patient’s age, and it will not differ? There is the CardioChek system where you can easily check the INR level in small babies.

Dr van Doorn: I think it probably will. And I think that it’s been well shown that with home anticoagulation testing you have a tighter control of the INR.

The other thing we’ve actually done, initially our mitral valves were anticoagulated with an INR between 2.5 and 3.5. And for the last few years, we’ve been running more between 2.0 and 3.0. And it seems that in particular in children bleeding is much more an adverse event as compared to thromboembolism, probably related to the fact that most children are in sinus rhythm and have a high heart rate, and therefore have very few other associated risk factors for thromboembolism.

Dr Wojtalik: And the second question, knowing about the results in the young age group, below 2 years of age, with mechanical valve, would you advise to implant a biologic valve, calculating redo surgery within a few years?

Dr van Doorn: We won’t, because the longevity of any bioprosthetic valve in a very young child is still short. This is actually a historical series, and I think nowadays we are much better at preserving the valves; and therefore, I think we’re unlikely to implant so many mechanical valves in young children at this moment in time.

Dr D. Lindblom (Stockholm, Sweden): I was wondering about those patients where you did a mitral valve re-replacement for patient-prosthesis mismatch. How much were you able to increase the size? How much bigger valve could you implant the second time? And what did you do to accommodate the larger prosthetic valve?

Dr van Doorn: We could always increase the size of the valve prosthesis at least by going the next size up. Some of the valves that were taken out were old tilting disk valves and were replaced with a bileaflet valve which has a better hemodynamic profile and an improved external-to-internal valve orifice area.

And there was also quite frequently pannus which we excised.

But generally, if you very carefully take out the old valve and you take great care to completely debride the annulus from any old suture material, you will actually get a bigger size valve in without too many problems.

Dr M. Mazen (Geza, Egypt): I want to ask you about pregnancy. Would you prefer to change anticoagulation to heparin, or fractionated heparin, or do you continue with warfarin?

Dr van Doorn: In the past, we would change to intravenous heparin, but actually we’re getting much happier using the subcutaneous heparin now. It seems to give adequate anticoagulation but much less bleeding events. A number of the bleeding events we had, were actually in children that came for a noncardiac surgical procedure who were put on heparin and then subsequently bled. So I think we’re getting a little more comfortable dropping the INR and using nonfractionated heparin rather than putting everyone on intravenous heparin.

Dr C. Pizarro (Wilmington, Delaware, USA): Did you notice any difference in the incidence of bleeding complications in younger patients versus older patients within your series, or the risk was pretty much linear? We have the impression that it’s more challenging to properly anticoagulate patients under 2 years of age.

The other question is, could you elaborate more about the poor correlation observed between symptoms and the hemodynamic data and what was the main indication for the reoperation of the patients who had a redo valve.

Dr van Doorn: With regards to the anticoagulation in small children, many infant feeds contain vitamin K derivatives, and I think that’s one of the reasons why these children are so difficult to anticoagulate.

On the other hand, in small children it is the parents who are in control of the blood tests and the tablets, so that offsets that to a small extent. But I think particularly if the child is sick, they’ve got some hepatic dysfunction, and if you’re not quite sure what goes in the feed or the diet changes, it may be fairly difficult.

With regards to the lack of correlation between the echo findings and the clinical symptoms, we’ve had children who, say, on echo Doppler had a peak inflow gradient, over the valve of 20 mmHg, who seem to be having quite a good exercise ability, whilst you would say that it’s probably time to replace that valve. And these children sometimes carry on for another couple of years.

Whilst, on the other hand, you have children with a much lower inflow gradient who were well when seen in the clinic 2 months earlier, who suddenly come in with an episode of acute pulmonary edema related to prosthetic valve dysfunction, and completely recover once you’ve put a new valve in. So that was what I was really referring to.

Dr P. Burczynski (Warsaw, Poland): This is a really long list of such difficult patients.

I wonder if you remember how many patients in this group has previous AV canal diagnosis.

Dr van Doorn: I think there were probably about 5 or 6 patients who had a complete AV canal, and there were also 3 or 4 partial canals. And in particular, the small AV canals that were repaired at between 3 and 6 months of age, some of those patients ended up with prosthetic mitral valves. If I look at our current experience, we hardly ever need to replace the valve when we’re repairing a canal.