



Use of mechanical valve prostheses in adults with tetralogy of Fallot

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ABSTRACT

Background: There are limited data about the outcomes mechanical prostheses in adults with tetralogy of Fallot (TOF). The purpose of the study was to describe the incidence of mechanical valve related adverse events (MVRAE), reoperation and all-cause mortality in TOF patients with mechanical valve prostheses.

Methods: We reviewed the MACHD (Mayo Adult Congenital Heart Disease) database and identified all adult TOF patients with mechanical valve prostheses, 1990–2017. MVRAE was defined as valve thrombosis, endocarditis, embolic stroke or major bleeding complications.

Results: A total of 44 prostheses were implanted in 29 patients (age 44 ± 13 years; men 18 [62%]), and 10 (36%) patients received multiple mechanical prostheses. The median number of prior sternotomies was 3 (range 2–7). Target intentional normalized ratio (INR) was 2.0–3.0 for patients with isolated mechanical aortic prostheses ($n = 12$, 41%), 2.5–4.0 for mechanical prostheses in non-aortic positions. There were no surgical deaths, and 10 MVRAE (endocarditis [$n = 4$], major bleeding complications [$n = 5$] and valve thrombosis [$n = 1$]) occurred in 7 (24%) patients during a median follow-up of 11 (5–18) years. The 10-year survival and freedom from reoperation were 87% and 95% respectively.

Conclusions: Surgical mortality and valve thrombosis for mechanical valve prostheses are low presumably due to appropriate patient selection and meticulous anticoagulation. Endocarditis and bleeding complications are major concerns. Further studies are required to determine the appropriate target INR that provides the optimal balance between preventing valve thrombosis and avoiding major bleeding complications mechanical valve prostheses in different positions.

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1. Introduction

Adults with repaired tetralogy of Fallot (TOF) often require reoperations for residual or recurrent hemodynamic lesions, and pulmonary valve regurgitation is the most common indication for reoperation [1–3]. The guidelines for management of valvular heart disease recommend mechanical prostheses for left-sided lesions in patients <60 years of age in order to avoid multiple reoperations due to structural failure [4,5]. However bioprosthetic valve remains the preferred valve prosthesis for tricuspid and pulmonary valve lesions because of a higher risk of thrombosis with mechanical prosthesis due to low pressure circulation in the right heart [6,7]. Unfortunately, bioprosthetic valves have limited longevity due to structural failure, and are also at risk for valve thrombosis, which often results in an increased lifetime

risk of reoperations [1–3]. Each subsequent reoperation becomes more technically challenging and carries a higher risk of morbidity and mortality [3]. Mechanical prostheses are sometimes used in TOF patients that are considered to be at significantly higher risk for future reoperations or in patients who are already on anticoagulation for other indications [8,9]. There are limited data about the use mechanical prostheses in adults with congenital heart disease, and there are no studies that specifically reviewed outcomes of mechanical prostheses in the different valve positions in patients with TOF [9,10]. The purpose of the study was to describe the incidence of mechanical valve related adverse events (MVRAE), reoperation and all-cause mortality in TOF patients with mechanical valve prostheses.

2. Methods

2.1. Patient selection and data collection

The MACHD (Mayo Adult Congenital Heart Disease) database was queried for patients (age ≥ 18 years) with repaired TOF followed at Mayo Clinic Rochester, Minnesota from January 1, 1990 through December 31, 2017. We selected all patients that already had mechanical valve prostheses and/or underwent implantation of mechanical valve

Abbreviations: TOF, Tetralogy of Fallot; MVRAE, Mechanical valve related adverse event; INR, International normalized ratio.

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prostheses at Mayo Clinic Rochester, Minnesota within the study period. The patients with pulmonary atresia were excluded. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization.

2.2. Endpoints and definitions

A composite endpoint of MVRAE was defined as valve thrombosis, endocarditis, embolic stroke or major bleeding complications. Valve thrombosis was defined as the presence of thrombus/vegetation on the valve prosthesis documented on echocardiogram and/or evidence of prosthesis dysfunction defined as a 50% increase in mean gradient and/or progression of prosthetic regurgitation compared to the post-implantation baseline echocardiogram [11,12]. A major bleeding complication was defined as intracranial bleeding, intra-thoracic or intra-abdominal hematoma requiring drainage or arterial embolization, or any bleeding complication with a decrease in hemoglobin >2 g/L and/or requiring transfusion of blood products [13]. The definition of embolic stroke and endocarditis are similar to previous studies [14,15].

Prosthetic valve function was assessed using transthoracic echocardiogram at the time of hospital discharge after prostheses implantation (baseline), at 1 year and at 5 years. We restricted the analysis of prosthetic valve function only to the valve prostheses that were implanted at Mayo Clinic within the study because of the lack of (or inconsistent availability) of baseline echocardiographic data for the prostheses implanted at outside institutions or before the beginning of the study. The severity of prosthesis stenosis was quantitatively assessed using the mean gradient, and the severity of prosthetic and periprosthetic regurgitation was qualitatively assessed (as none/trivial, mild, mild/moderate, moderate, moderate/severe, and severe) as stipulated in the guidelines of the American Society of Echocardiography [16]. Effective orifice area was calculated for aortic valve prostheses using the continuity equation [16,17]. Effective orifice area was not analyzed for the other prosthesis positions because the necessary hemodynamic measurements were not consistently acquired in all patients.

2.3. Statistical analysis

Data were presented as mean \pm standard deviation, median (interquartile range) or counts (%). Student *t*-test, Analysis of Variance test, χ^2 or Fisher's exact test (as appropriate) were used to compare between-group differences. Freedom from MVRAE was assessed using the Kaplan Meier method, and the time of the first mechanical valve prosthesis implantation was used as 'time zero' for each patient. Only one MVRAE was counted per patient for the assessment of composite endpoint, and the time of the first MVRAE was used in the Kaplan Meier analysis for the patients that had more than one event. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc., Cary NC) and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 29 (6%) consecutive patients with mechanical valve prostheses out of 465 adult TOF patients were selected for the study. The age at the time of valve implantation was 44 ± 13 years and 18 (62%) were men. The interval between TOF repair and initial mechanical valve implantation was 37 ± 9 years. A comparison of the baseline clinical and hemodynamic data of the 29 patients with mechanical prostheses and the rest of the TOF cohort is shown in Supplementary Tables 1 and 2.

A total of 44 prostheses were implanted in 29 patients. Of these, 4 prostheses in 4 patients were implanted prior to the beginning of the study or implanted at an outside institution prior to the first presentation to Mayo Clinic. The clinical data of these 4 patients/prostheses are as follows: the first patient underwent aortic valve replacement with a Bjork Shiley valve (Pfizer, New York, NY) at the age of 17 years for aortic stenosis and a re-do aortic valve replacement at age 50 years with a 23 mm CarboMedics mechanical prosthesis (Liva-Nova, London, United Kingdom) for prosthetic valve endocarditis. The second patient underwent aortic valve replacement with 10A Starr-Edwards valve (Edwards LifeSciences) at the age of 19 years for bicuspid aortic valve and aortic regurgitation. The patient had re-do reoperation for aortic valve replacement with 21 mm CarboMedics mechanical prosthesis (Liva-Nova, London, United Kingdom) at the time of bioprosthetic pulmonary valve replacement at the age of 48 years. The third patient initially had aortic valve replacement with 11A Starr-Edwards mechanical prosthesis (Edwards LifeSciences) at the age of 22 years because of aortic regurgitation. He subsequently developed aortic root aneurysm measuring 72 mm for which he had aortic valve and root replacement

with 25 mm CarboMedics valve conduit (Liva-Nova, London, United Kingdom) and coronary artery bypass grafting at the age of 55 years. The fourth patient had aortic valve replacement with a 23 mm St Jude mechanical prosthesis (St Paul, Minneapolis) at the age of 48 years at an outside institution and required another aortic and pulmonary valve replacement with mechanical prostheses at Mayo Clinic because of prosthetic valve endocarditis at the age of 66 years.

3.2. Mechanical valve prostheses

Of the 40 prostheses that were implanted at Mayo Clinic within the study, the mean cardiopulmonary bypass time and cross clamp time were 192 ± 53 and 71 ± 26 min respectively. The median number of prior sternotomies was 3 (range 2–7). The types of prostheses implanted were St Jude valve prostheses ([St Paul, Minneapolis]; $n = 15$, 38%), CarboMedics valve prostheses ([Liva-Nova, London, United Kingdom]; $n = 21$, 53%), and On-X prostheses ([CryoLife Inc., Kennesaw, Ga]; $n = 4$, 10%). The sizes of the prostheses were 25 ± 2 mm (aortic, $n = 21$ [53%]), 30 ± 3 mm (mitral, $n = 6$ [15%]), 29 mm (tricuspid, $n = 2$ [5%]), and 27 ± 3 mm (pulmonary, $n = 11$ [28%]). The indication for mechanical valve implantation in the tricuspid and pulmonary positions was because of multiple (>3) prior sternotomies. There were 10 (36%) patients that received multiple prostheses (concomitantly at the time of surgery) and the different combinations of prostheses were as follows: aortic and pulmonary prostheses ($n = 6$); aortic, tricuspid, and pulmonary prostheses ($n = 1$); mitral and pulmonary prostheses ($n = 1$); mitral and tricuspid prostheses ($n = 1$); and aortic and mitral prostheses ($n = 1$), Supplementary Table 3.

The average length of hospital stay was 7 ± 2 days. All patients received warfarin for anticoagulation, and the target intentional normalized ratio (INR) was 2.0–3.0 in 12 (41%) patients with isolated mechanical aortic prostheses, 2.5–3.5 in 15 (52%) patients with mechanical prostheses in the mitral or pulmonary positions, and 3.0–4.0 in 2 (7%) patients with mechanical prostheses in the tricuspid position.

All patients had baseline transthoracic echocardiograms at the time of hospital discharge, while 26 patients and 19 patients had echocardiograms at 1-year and 5-years postoperative follow-up. The baseline mean gradients were 12 ± 2 mm Hg (aortic), 14 ± 3 mm Hg (pulmonary), 4 ± 1 mm Hg (mitral), and 5 mm Hg (tricuspid). All patients had mild (or less) prosthetic and/or periprosthetic regurgitation except for one patient that had mild/moderate periprosthetic regurgitation of the aortic prosthesis. There was no significant change in prosthesis gradient or severity of prosthetic/periprosthetic regurgitation over time (Fig. 1). Similarly there was no significant difference in the effective orifice area of the aortic valve prostheses during follow-up, 1.8 ± 0.3 cm² (baseline) vs 1.9 ± 0.3 cm² (1 year) vs 1.7 ± 0.2 cm² (5 years), $p = 0.265$.

3.3. Mechanical valve related adverse events

Of the 44 prosthesis implanted in 29 patients, there were 10 MVRAE in 7 (24%) patients during a median follow-up of 11 [5–18] years. These MVRAE were prosthetic valve endocarditis ($n = 4$), major bleeding complications ($n = 5$), and mechanical valve thrombosis ($n = 1$). There were no embolic strokes. The clinical data of the 7 patients with MVRAE are as follow: Patient #1 was a 38-year old male with aortic, tricuspid and pulmonary mechanical valve prostheses who had *Corynebacterium* septicemia and prosthetic valve endocarditis and received medical therapy alone because he was deemed inoperable because of multiple comorbidities. He had good response to medical therapy but had recurrence of endocarditis 2 years later resulting in death from multi-system organ failure. Patient #2 was a 49-year old male with mechanical mitral valve prosthesis who had spontaneous subdural hematoma that was managed conservatively. He also had a large hematoma in the right thigh (requiring percutaneous drainage) secondary to a

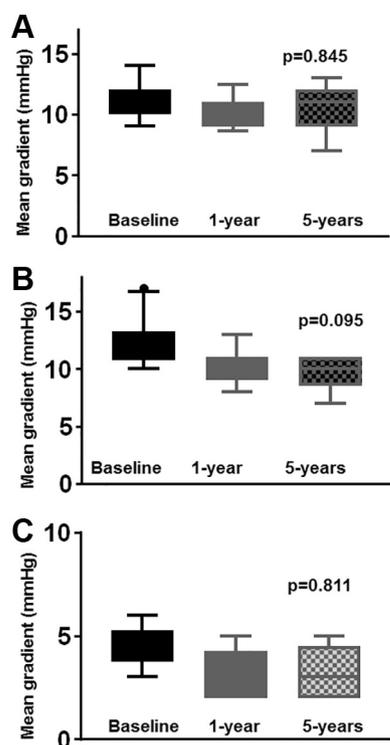


Fig. 1. Outlier boxplots showing valve gradients for aortic (A), pulmonary (B) and mitral (C). This shows the mean prosthetic valve gradients at different time points from baseline (black), through 1-year follow-up (gray) to 5-years follow-up (checkers). *p* values represent temporal changes in gradient for each valve position. Note that tricuspid valve prosthesis was not plotted because of very few number of tricuspid prosthesis in this study.

mechanical fall 8 years later. The patient died at the age of 57 years from end-stage heart failure. Patient #3 was a 43-year old male with mechanical aortic valve prosthesis who had an episode of massive gastrointestinal bleeding requiring multiple blood transfusions and died (unwitnessed sudden cardiac death) 3 days later. Patient #4 was a 66-year old man with mechanical aortic valve prosthesis who had enterococcus endocarditis resulting in severe periprosthetic aortic and pulmonary regurgitation requiring reoperation for aortic and pulmonary valve replacement with mechanical prostheses. He died 2 months after surgery because recurrence of enterococcus sepsis leading to multi-system organ failure. Patient #5 was a 43-year old male with mechanical aortic valve prosthesis who had iliopsoas hematoma requiring surgical drainage, and also had an episode of massive gastrointestinal bleeding requiring multiple blood transfusions 3 months later. Patient #6 is a 50-year old man with mechanical aortic valve who developed prosthetic valve endocarditis requiring reoperation for aortic valve replacement with mechanical prosthesis. Patient #7 is a 24-year old female with mechanical pulmonary valve who had mechanical valve thrombosis in the setting of subtherapeutic INR of 1.6 due to noncompliance. She received thrombolytic therapy with some improvement in valve function but continued to have severe pulmonary regurgitation and subsequent pulmonary valve replacement with a bioprosthesis.

Of the 5 major bleeding events observed in this series, only one occurred in the setting of INR > 3.5. The freedom from MVRAE was 88% and 59% at 10 and 20 years respectively while the freedom from reoperation was 95% and 66% at 10 and 20 years respectively (Fig. 2). There were 6 (21%) deaths due to the following causes: end-stage heart failure (*n* = 2), sudden cardiac death (*n* = 1); sepsis and multi-system organ failure (*n* = 2), and unknown (*n* = 1). The 10-year and 20-year survival were 87% and 59% respectively.

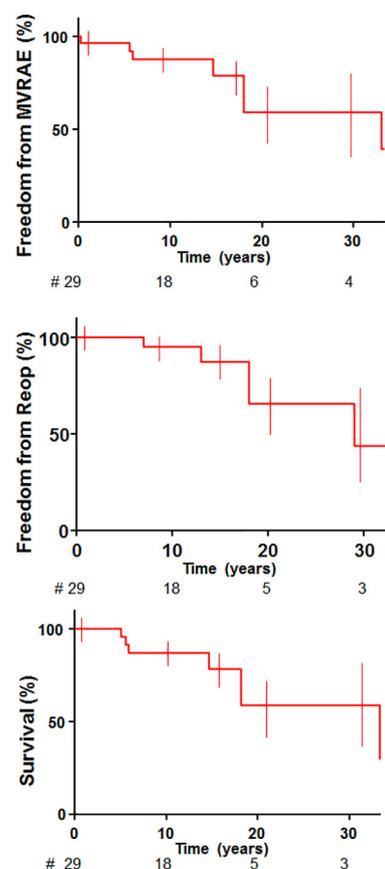


Fig. 2. Kaplan Meier curves showing the freedom from MVRAE (top), freedom from reoperation (middle) and survival (bottom). MVRAE: mechanical valve related adverse events; Reop: reoperation.

4. Discussion

In the study, we reviewed outcomes of mechanical prostheses in 29 adult TOF patients, and the 10-year survival and freedom from reoperation were 87% and 95% respectively. MVRAE occurred in 24% of the cohort and these events were due to endocarditis, major bleeding complications and mechanical valve thrombosis. The need for multiple reoperations for residual or recurrent valvular heart lesions is a major challenge in the management of adults with repaired TOF [1–3]. While bioprosthetic valves are generally preferred for the treatment of right-sided valvular lesions in an effort to avoid long-term anticoagulation [1–3], mechanical valve prostheses are sometimes used in selected patients [6–8]. The freedom from reintervention in TOF patients with prior bioprosthetic valve implantation is less 70% at 20 years [2,3,18]. Such patients include those with multiple prior cardiac surgeries that are deemed high risk for future reoperations, and patients that are already on anticoagulation for a mechanical prostheses or atrial arrhythmia [6–8].

Outcomes data for mechanical valve prostheses in TOF patients are limited [9,10]. In a large retrospective multicenter study of 364 adults with congenital heart disease that underwent implantation of mechanical valve prostheses in the pulmonary position, Pragt et al. reported a 10-year survival and freedom from reoperation of 91% and 91% respectively, and 10% of their cohort had mechanical valve thrombosis [9]. The excellent midterm survival and freedom from reoperation reported in the Pragt et al. study was similar to the results of the current study, although mechanical valve thrombosis was more common in their cohort (10% vs 4%). We suspect that the higher incidence of mechanical valve thrombosis in their cohort may be related to suboptimal anticoagulation because only 65% of their patients were on warfarin. In a different study of 66 patients with mechanical valve prostheses in the pulmonary

position, the 10-year survival and freedom from reoperation of 81% and 89% respectively, and again 10% of the patients had mechanical valve thrombosis, yielding an annual thrombosis rate of 1.5% per year [19]. All the cases of mechanical valve thromboses in that study occurred either in the setting of suboptimal anticoagulation or no anticoagulation at all. In another study of 37 pediatric and young adult patients (median age 14 years) with mechanical pulmonary valve prostheses, the 10-year survival and freedom from reoperation was 97% and 88% respectively [10]. Mechanical valve thrombosis occurred in 3 (8%) patients and was related to suboptimal anticoagulation.

In contrast to all these studies [9,10,19], the incidence of mechanical valve thrombosis was somewhat lower in our cohort, and we speculated that this may be related to a more aggressive anticoagulation practice at our institution. All patients with mechanical valves receive lifelong anticoagulation with warfarin, and we aim for a higher INR target if the mechanical valve prosthesis is in a non-aortic position with a recommended INR of 2.5–3.5 for pulmonary valve prosthesis and 3.0–4.0 for tricuspid valve prosthesis. All patients are also advised to take low dose aspirin, as suggested by the valve practice guidelines [4]. The only case of mechanical valve thrombosis in this study occurred in the setting of subtherapeutic INR in a patient who was not compliant with anticoagulation therapy. A potential downside of this approach will be a higher risk of bleeding complications, and we observed 5 major bleeding complications in 3 (11%) patients. Interestingly, only 1 of the 5 major bleeding complications occurred in the setting of INR > 3.5, suggesting that there may be other patient-specific factors contributory to these bleeding complications. Unlike the previous studies that reported early surgical mortality of 2% to 5% and no cases of endocarditis [9,19–21], there was no early surgical mortality in the current study, and prosthetic valve endocarditis occurred in 11% of our cohort. While the cause of the higher incidence of prosthetic valve endocarditis in the current study is not readily apparent, the low surgical mortality may be related to appropriate patient selection and cumulative expertise due to high annual volume of congenital cardiac operations and reoperations which is known to be associated with comparatively lower surgical mortality [22].

All previous studies of outcomes of mechanical valve prosthesis in adult congenital heart disease have been conducted in patients with mechanical valve in the pulmonary position [9,19–21]. The current study is novel because it provides outcome data about the performance and complications of mechanical valve prostheses (in all positions) in TOF patients. The data are clinically relevant because one-third of the patients in the study had mechanical valve prostheses in more than one position. A bioprosthetic valve is preferred for right-sided valvular lesion because of concerns about mechanical valve thrombosis. While this concern is valid, the current study suggests that the risk of thrombosis may be mitigated, at least to some extent, by meticulous anticoagulation administration and monitoring. Another important fact that is often overlooked is that valve thrombosis can also occur in patients with bioprosthetic valves, and these patients may require lifelong anticoagulation if bioprosthetic valve thrombosis occurs [11,12,23]. The risks and benefits of mechanical valve prostheses for right-sided valvular lesions should be thoroughly discussed with the appropriate patients (patients at high surgical risk for future reoperation and patients that already have left-sided mechanical prostheses) in order to empower the patient to make informed decisions.

A major limitation of this study is the small sample size which prohibited more in-depth subgroup analysis. The study may also be influenced by selection bias since it was conducted in a congenital heart disease referral center, and this limits generalizability of the results. However the major take home message is that mechanical valve prosthesis may be an appropriate option in some TOF patients, and that surgical mortality and incidence of valve thrombosis may be low with appropriate patient selection and meticulous anticoagulation administration in conjunction with aspirin. Further studies are required to determine the appropriate target INR that provides the optimal

balance between preventing valve thrombosis and avoiding major bleeding complications in patients with right-sided mechanical valve prostheses.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.02.028>.

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